# FIRST AID FOR THE® USMLE® STEP 1 2021

A STUDENT-TO-STUDENT GUIDE

**Updated study advice** for Step 1 success

**All new communication skills section** reflects the new Step 1 blueprint

**Nearly 1,400 must-know concepts** with many new high-yield facts

**Expanded illustrations, tables, and mnemonics** to help you retain key information

**Student-proven exam strategies** to boost your score

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**First Aid for the® USMLE Step 1 2021: A Student-to-Student Guide**



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**Notice**

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

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The editors were Bob Boehringer and Christina M. Thomas.
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This book is printed on acid-free paper.

## Dedication

To all healthcare workers and first responders worldwide leading the fight against COVID-19. We salute your ongoing efforts and honor those who have lost their lives in service to others.

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# Foreword

*"If you see something that is not right, not fair, not just, you have a moral obligation to do something."*

Congressman John Lewis

*First Aid for the USMLE Step 1* began over 30 years ago as a resource to prepare aspiring physicians for their first medical board exam. Since then, it has become one of the most well-known textbooks used by medical students worldwide. While we closely follow the USMLE's lead in most respects, the widespread use of our book also provides an opportunity for us to be leaders in medical education.

In prior editions, there has been an unfortunate absence of diversity in both the text and images. This year, we strongly affirm that representing a broad spectrum of patients is essential for preparing for a successful medical career. The practice of medicine is inextricably intertwined with social determinants of health, and sociocultural understanding complements scientific knowledge for the future physician. Failing to provide representation of a diversity of people limits the educational experience and is to the detriment of future patients. We here describe our approach to improving the representation of race, ethnicity, sex, and gender, recognizing that we are neither experts nor authorities on diversity, equity, and inclusion.

We first surveyed our existing visual depictions of patients and pathologies. Of nearly 70 illustrations showing skin tone or sex in the 2020 edition, every single one showed pink/light beige skin, and all but one was male-appearing, excluding reproductive anatomy illustrations. To address this lack of diversity, we revised our illustrations to better reflect Fitzpatrick skin types I-VI and introduced more female-appearing and gender-neutral illustrations.

We also reviewed our use of language in the text. With respect to race and ethnicity, we transitioned from using "African-American" to "Black," as not all Black patients are American or have African ancestry. We now capitalize "Black" in accordance with major journalistic organizations. We also switched from "Caucasian" to "White," which we hope will be more accurate and inclusive.

We found many opportunities to improve the language used to describe disabled and ill patients as well. We now use person-first language such as "patients with diabetes" instead of "diabetic patients." Dated references to "mental retardation" have been replaced with "intellectual disability." We also removed other stigmatizing terms such as "alcoholics," "smokers," "epileptics," and "bulimics" and replaced with appropriate person-first language.

Finally, we reviewed our use of terminology surrounding sex and gender identity. We opted for more neutral language by changing most uses of gendered pronouns to "they/them/theirs," as well as changing "mother" to "pregnant patient." We also removed gendered terms such as "girl," "boy," "woman," and "man" in favor of "female" and "male" when referring to biological sex.

We acknowledge that our approach is imperfect and challenges remain. We also recognize that there may be differing perspectives that need to be addressed and balanced. However, just as the medical community learns invaluable lessons from its patients, we greatly value input from our peers and colleagues. We enthusiastically encourage feedback on our efforts to better represent all people. If you have comments or suggestions, please submit them via our website at **www.firstaidteam.com**. Alternatively, you can email us at **firstaid@scholarrx.com**. Thank you for your help in making *First Aid for the USMLE Step 1* an increasingly inclusive and useful resource.

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# Preface

With the 31st edition of *First Aid for the USMLE Step 1*, we continue our commitment to providing students with the most useful and up-to-date preparation guide for the USMLE Step 1. This edition represents an outstanding revision in many ways, including:

- 104 entirely new or heavily revised high-yield topics reflecting evolving trends in the USMLE Step 1.
- Updated ethics section and introduction of new communications skills section to reflect the recently changed Step 1 exam.
- Extensive text revisions, new mnemonics, clarifications, and corrections curated by a team of 25 medical student and resident physician authors who excelled on their Step 1 examinations and verified by a team of expert faculty advisors and nationally recognized USMLE instructors.
- Updated with 179 new and revised diagrams and illustrations as part of our ongoing collaboration with USMLE-Rx and ScholarRx (MedIQ Learning, LLC).
- Updated with 62 new and revised photos to help visualize various disorders, descriptive findings, and basic science concepts. Additionally, revised imaging photos have been labeled and optimized to show both normal anatomy and pathologic findings.
- Updated exam preparation advice for USMLE Step 1 pass/fail, Step 1 blueprint changes, and COVID-19 impacts.
- Revised language to support diversity, equity, and inclusion.
- Updated study tips on the opening page of each chapter.
- Improved organization and integration of text, illustrations, clinical images, and tables throughout for focused review of high-yield topics.
- Revised and expanded ratings of current, high-yield review resources, with clear explanations of their relevance to USMLE review.
- Real-time Step 1 updates and corrections can be found exclusively on our blog, www.firstaidteam.com.

We invite students and faculty to share their thoughts and ideas to help us continually improve *First Aid for the USMLE Step 1* through our blog and collaborative editorial platform. (See How to Contribute, p. xvii.)

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# General Acknowledgments

Each year we are fortunate to receive the input of thousands of medical students and graduates who provide new material, clarifications, and potential corrections through our website and our collaborative editing platform. This has been a tremendous help in clarifying difficult concepts, correcting errata from the previous edition, and minimizing new errata during the revision of the current edition. This reflects our long-standing vision of a true, student-to-student publication. We have done our best to thank each person individually below, but we recognize that errors and omissions are likely. Therefore, we will post an updated list of acknowledgments at our website, www.firstaidteam.com/bonus/. We will gladly make corrections if they are brought to our attention.

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# How to Contribute

This edition of *First Aid for the USMLE Step 1* incorporates thousands of contributions and improvements suggested by student and faculty advisors. We invite you to participate in this process. Please send us your suggestions for:

- Study and test-taking strategies for the USMLE Step 1
- New facts, mnemonics, diagrams, and clinical images
- High-yield topics that may appear on future Step 1 exams
- Personal ratings and comments on review books, question banks, apps, videos, and courses

For each new entry incorporated into the next edition, you will receive **up to a $20 Amazon.com gift card** as well as personal acknowledgment in the next edition. Significant contributions will be compensated at the discretion of the authors. Also, let us know about material in this edition that you feel is low yield and should be deleted.

All submissions including potential errata should ideally be supported with hyperlinks to a dynamically updated Web resource such as UpToDate, AccessMedicine, and ClinicalKey.

We welcome potential errata on grammar and style if the change improves readability. Please note that *First Aid* style is somewhat unique; for example, we have fully adopted the *AMA Manual of Style* recommendations on eponyms ("We recommend that the possessive form be omitted in eponymous terms") and on abbreviations (no periods with eg, ie, etc). We also avoid periods in tables unless required for full sentences. Kindly refrain from submitting "style errata" unless you find specific inconsistencies with the *AMA Manual of Style* or our diversity initiative as discussed in the Foreword.

The preferred way to submit new entries, clarifications, mnemonics, or potential corrections with a valid, authoritative reference is via our website: **www.firstaidteam.com**.

This website will be continuously updated with validated errata, new high-yield content, and a new online platform to contribute suggestions, mnemonics, diagrams, clinical images, and potential errata.

Alternatively, you can email us at: **firstaid@scholarrx.com.**

Contributions submitted by **May 15, 2021**, receive priority consideration for the 2022 edition of *First Aid for the USMLE Step 1*. We thank you for taking the time to share your experience and apologize in advance that we cannot individually respond to all contributors as we receive thousands of contributions each year.

## NOTE TO CONTRIBUTORS

All contributions become property of the authors and are subject to editing and reviewing. Please verify all data and spellings carefully. Contributions should be supported by at least two high-quality references.

Check our website first to avoid duplicate submissions. In the event that similar or duplicate entries are received, only the first complete entry received with valid, authoritative references will be credited. Please follow the style, punctuation, and format of this edition as much as possible.

## JOIN THE FIRST AID TEAM

The *First Aid*/ScholarRx team is pleased to offer paid editorial and coaching positions. We are looking for passionate, experienced, and dedicated medical students and recent graduates. Participants will have an opportunity to work on a wide variety of projects, including the popular *First Aid* series and the growing line of USMLE-Rx/ScholarRx products, including Rx Bricks. Please use our webform at https://www.usmle-rx.com/join-the-first-aid-team/ to apply, and include a CV and writing examples.

For 2021, we are actively seeking passionate medical students and graduates with a specific interest in improving our medical illustrations, expanding our database of photographs (including clinical images depicting diverse skin types), and developing the software that supports our crowdsourcing platform. We welcome people with prior experience and talent in these areas. Relevant skills include clinical imaging, digital photography, digital asset management, information design, medical illustration, graphic design, tutoring, and software development.

# How to Use This Book

**CONGRATULATIONS:** You now possess the book that has guided nearly two million students to USMLE success for over 30 years. With appropriate care, the binding should last the useful life of the book. Keep in mind that putting excessive flattening pressure on any binding will accelerate its failure. If you purchased a book that you believe is defective, please **immediately** return it to the place of purchase. If you encounter ongoing issues, you can also contact Customer Service at our publisher, McGraw Hill.

**START EARLY:** Use this book as early as possible while learning the basic medical sciences. The first semester of your first year is not too early! Devise a study plan by reading Section I: Guide to Efficient Exam Preparation, and make an early decision on resources to use by checking Section IV: Top-Rated Review Resources. Note that *First Aid* is neither a textbook nor a comprehensive review book, and it is not a panacea for inadequate preparation.

**CONSIDER *FIRST AID* YOUR ANNOTATION HUB:** Annotate material from other resources, such as class notes or comprehensive textbooks, into your book. This will keep all the high-yield information you need in one place. Other tips on keeping yourself organized:

- For best results, use fine-tipped ballpoint pens (eg, BIC Pro+, Uni-Ball Jetstream Sports, Pilot Drawing Pen, Zebra F-301). If you like gel pens, try Pentel Slicci, and for markers that dry almost immediately, consider Staedtler Triplus Fineliner, Pilot Drawing Pen, and Sharpies.
- Consider using pens with different colors of ink to indicate different sources of information (eg, blue for USMLE-Rx Step 1 Qmax, green for UWorld Step 1 Qbank).
- Choose highlighters that are bright and dry quickly to minimize smudging and bleeding through the page (eg, Tombow Kei Coat, Sharpie Gel).
- Many students de-spine their book and get it 3-hole-punched. This will allow you to insert materials from other sources, including curricular materials.

**INTEGRATE STUDY WITH CASES, FLASH CARDS, AND QUESTIONS:** To broaden your learning strategy, consider integrating your *First Aid* study with case-based reviews (eg, *First Aid Cases for the USMLE Step 1*), flash cards (eg, USMLE-Rx Step 1 Flash Facts), and practice questions (eg, the USMLE-Rx Step 1 Qmax). Read the chapter in the book, then test your comprehension by using cases, flash cards, and questions that cover the same topics. Maintain access to more comprehensive resources (eg, ScholarRx Bricks and USMLE-Rx Step 1 Express videos) for deeper review as needed.

**PRIME YOUR MEMORY:** Return to your annotated Sections II and III several days before taking the USMLE Step 1. The book can serve as a useful way of retaining key associations and keeping high-yield facts fresh in your memory just prior to the exam. The Rapid Review section includes high-yield topics to help guide your studying.

**CONTRIBUTE TO FIRST AID:** Reviewing the book immediately after your exam can help us improve the next edition. Decide what was truly high and low yield and send us your comments. Feel free to send us scanned images from your annotated *First Aid* book as additional support. Of course, always remember that **all examinees are under agreement with the NBME to not disclose the specific details of copyrighted test material.**

# Selected USMLE Laboratory Values

* = Included in the Biochemical Profile (SMA-12)

| Blood, Plasma, Serum | Reference Range | SI Reference Intervals |
|---|---|---|
| *Alanine aminotransferase (ALT, GPT at 30°C) | 10–40 U/L | 10–40 U/L |
| *Alkaline phosphatase | 25–100 U/L | 25–100 U/L |
| Amylase, serum | 25–125 U/L | 25–125 U/L |
| *Aspartate aminotransferase (AST, GOT at 30°C) | 12–38 U/L | 12–38 U/L |
| Bilirubin, serum (adult)<br>Total // Direct | <br>0.1–1.0 mg/dL // 0.0–0.3 mg/dL | <br>2–17 µmol/L // 0–5 µmol/L |
| *Calcium, serum (Total) | 8.4–10.2 mg/dL | 2.1–2.6 mmol/L |
| *Cholesterol, serum (Total) | Rec: < 200 mg/dL | < 5.2 mmol/L |
| *Creatinine, serum (Total) | 0.6–1.2 mg/dL | 53–106 µmol/L |
| Electrolytes, serum<br>Sodium ($Na^+$)<br>Chloride ($Cl^-$)<br>* Potassium ($K^+$)<br>Bicarbonate ($HCO_3^-$)<br>Magnesium ($Mg^{2+}$) | <br>136–146 mEq/L<br>95–105 mEq/L<br>3.5–5.0 mEq/L<br>22–28 mEq/L<br>1.5–2 mEq/L | <br>136–146 mmol/L<br>95–105 mmol/L<br>3.5–5.0 mmol/L<br>22–28 mmol/L<br>0.75–1.0 mmol/L |
| Gases, arterial blood (room air)<br>$P_{O_2}$<br>$P_{CO_2}$<br>pH | <br>75–105 mm Hg<br>33–45 mm Hg<br>7.35–7.45 | <br>10.0–14.0 kPa<br>4.4–5.9 kPa<br>[$H^+$] 36–44 nmol/L |
| *Glucose, serum | Fasting: 70–100 mg/dL | 3.8–6.1 mmol/L |
| Growth hormone – arginine stimulation | Fasting: < 5 ng/mL<br>Provocative stimuli: > 7 ng/mL | < 5 µg/L<br>> 7 µg/L |
| Osmolality, serum | 275–295 mOsmol/kg $H_2O$ | 275–295 mOsmol/kg $H_2O$ |
| *Phosphorus (inorganic), serum | 3.0–4.5 mg/dL | 1.0–1.5 mmol/L |
| Prolactin, serum (hPRL) | Male: < 17 ng/mL<br>Female: < 25 ng/mL | < 17 µg/L<br>< 25 µg/L |
| *Proteins, serum<br>Total (recumbent)<br>Albumin<br>Globulins | <br>6.0–7.8 g/dL<br>3.5–5.5 g/dL<br>2.3–3.5 g/dL | <br>60–78 g/L<br>35–55 g/L<br>23–35 g/L |
| Thyroid-stimulating hormone, serum or plasma | 0.4–4.0 µU/mL | 0.4–4.0 mIU/L |
| *Urea nitrogen, serum (BUN) | 7–18 mg/dL | 25–64 nmol/L |
| *Uric acid, serum | 3.0–8.2 mg/dL | 0.18–0.48 mmol/L |

*(continues)*

| Cerebrospinal Fluid | Reference Range | SI Reference Intervals |
|---|---|---|
| Cell count | 0–5/$mm^3$ | 0–5 × $10^6$/L |
| Glucose | 40–70 mg/dL | 2.2–3.9 mmol/L |
| Proteins, total | < 40 mg/dL | < 0.40 g/L |
| **Hematologic** | | |
| Erythrocyte count | Male: 4.3–5.9 million/$mm^3$<br>Female: 3.5–5.5 million/$mm^3$ | 4.3–5.9 × $10^{12}$/L<br>3.5–5.5 × $10^{12}$/L |
| Erythrocyte sedimentation rate (Westergen) | Male: 0–15 mm/hr<br>Female: 0–20 mm/hr | 0–15 mm/hr<br>0–20 mm/hr |
| Hematocrit | Male: 41–53%<br>Female: 36–46% | 0.41–0.53<br>0.36–0.46 |
| Hemoglobin, blood | Male: 13.5–17.5 g/dL<br>Female: 12.0–16.0 g/dL | 135–175 g/L<br>120–160 g/L |
| Hemoglobin, plasma | < 4 mg/dL | < 0.62 µmol/L |
| Leukocyte count and differential | | |
| Leukocyte count | 4,500–11,000/$mm^3$ | 4.5–11.0 × $10^9$/L |
| Segmented neutrophils | 54–62% | 0.54–0.62 |
| Band forms | 3–5% | 0.03–0.05 |
| Eosinophils | 1–3% | 0.01–0.03 |
| Basophils | 0–0.75% | 0–0.0075 |
| Lymphocytes | 25–33% | 0.25–0.33 |
| Monocytes | 3–7% | 0.03–0.07 |
| Mean corpuscular hemoglobin | 25–35 pg/cell | 0.39–0.54 fmol/cell |
| Mean corpuscular hemoglobin concentration | 31%–36% Hb/cell | 4.8–5.6 mmol Hb/L |
| Mean corpuscular volume | 80–100 $\mu m^3$ | 80–100 fL |
| Partial thromboplastin time (activated) | 25–40 sec | 25–40 sec |
| Platelet count | 150,000–400,000/$mm^3$ | 150–400 × $10^9$/L |
| Prothrombin time | 11–15 sec | 11–15 sec |
| Reticulocyte count | 0.5–1.5% of RBCs | 0.005–0.015 |
| **Urine** | | |
| Creatinine clearance | Male: 97–137 mL/min<br>Female: 88–128 mL/min | 97–137 mL/min<br>88–128 mL/min |
| Osmolality | 50–1200 mOsmol/kg $H_2O$ | 50–1200 mOsmol/kg $H_2O$ |
| Proteins, total | < 150 mg/24 hr | < 0.15 g/24 hr |
| **Other** | | |
| Body mass index | Adult: 19–25 kg/$m^2$ | 19–25 kg/$m^2$ |

## First Aid Checklist for the USMLE Step 1

This is an example of how you might use the information in Section I to prepare for the USMLE Step 1. Refer to corresponding topics in Section I for more details.

**Years Prior**

- ☐ Use top-rated review resources for first-year medical school courses.
- ☐ Ask for advice from those who have recently taken the USMLE Step 1.

**Months Prior**

- ☐ Review computer test format and registration information.
- ☐ Register six months in advance.
- ☐ Carefully verify name and address printed on scheduling permit. Make sure the name on scheduling permit matches the name printed on your photo ID. Be familiar with COVID-19 cancellation and rescheduling policies.
- ☐ Go online for test date ASAP.
- ☐ Define your exam goals (pass comfortably, beat the mean, ace the test)
- ☐ Set up a realistic timeline for study. Cover less crammable subjects first.
- ☐ Evaluate and choose study materials (review books, question banks).
- ☐ Use a question bank to simulate the USMLE Step 1 to pinpoint strengths and weaknesses in knowledge and test-taking skills.

**Weeks Prior**

- ☐ Do test simulations in question banks.
- ☐ Assess how close you are to your goal.
- ☐ Pinpoint remaining weaknesses. Stay healthy (exercise, sleep).
- ☐ Verify information on admission ticket (eg, location, date).

**One Week Prior**

- ☐ Remember comfort measures (loose clothing, earplugs, etc).
- ☐ Work out test site logistics (eg, location, transportation, parking, lunch).
- ☐ Print or download your Scheduling Permit and Scheduling Confirmation to your phone.

**One Day Prior**

- ☐ Relax.
- ☐ Lightly review short-term material if necessary. Skim high-yield facts.
- ☐ Get a good night's sleep.

**Day of Exam**

- ☐ Relax.
- ☐ Eat breakfast.
- ☐ Minimize bathroom breaks during exam by avoiding excessive morning caffeine.

**After Exam**

- ☐ Celebrate, regardless of how well you feel you did.
- ☐ Send feedback to us on our website at **www.firstaidteam.com**.

SECTION I

# Guide to Efficient Exam Preparation

*"One important key to success is self-confidence. An important key to self-confidence is preparation."*

—Arthur Ashe

*"Wisdom is not a product of schooling but of the lifelong attempt to acquire it."*

—Albert Einstein

*"Finally, from so little sleeping and so much reading, his brain dried up and he went completely out of his mind."*

—Miguel de Cervantes Saavedra, *Don Quixote*

*"Sometimes the questions are complicated and the answers are simple."*

—Dr. Seuss

*"He who knows all the answers has not been asked all the questions."*

—Confucius

*"The expert in anything was once a beginner."*

—Helen Hayes

*"It always seems impossible until it's done."*

—Nelson Mandela

## ▸ INTRODUCTION

Relax.

This section is intended to make your exam preparation easier, not harder. Our goal is to reduce your level of anxiety and help you make the most of your efforts by helping you understand more about the United States Medical Licensing Examination, Step 1 (USMLE Step 1). As a medical student, you are no doubt familiar with taking standardized examinations and quickly absorbing large amounts of material. When you first confront the USMLE Step 1, however, you may find it all too easy to become sidetracked from your goal of studying with maximal effectiveness. Common mistakes that students make when studying for Step 1 include the following:

- Starting to study (including *First Aid*) too late
- Starting to study intensely too early and burning out
- Starting to prepare for boards before creating a knowledge foundation
- Using inefficient or inappropriate study methods
- Buying the wrong resources or buying too many resources
- Buying only one publisher's review series for all subjects
- Not using practice examinations to maximum benefit
- Not understanding how scoring is performed or what the score means
- Not using review books along with your classes
- Not analyzing and improving your test-taking strategies
- Getting bogged down by reviewing difficult topics excessively
- Studying material that is rarely tested on the USMLE Step 1
- Failing to master certain high-yield subjects owing to overconfidence
- Using *First Aid* as your sole study resource
- Trying to prepare for it all alone

In this section, we offer advice to help you avoid these pitfalls and be more productive in your studies.

▸ *The test at a glance:*

- *8-hour exam*
- *Up to a total of 280 multiple choice items*
- *7 test blocks (60 min/block)*
- *Up to 40 test items per block*
- *45 minutes of break time, plus another 15 if you skip the tutorial*

## ▸ USMLE STEP 1—THE BASICS

The USMLE Step 1 is the first of three examinations that you would normally pass in order to become a licensed physician in the United States. The USMLE is a joint endeavor of the National Board of Medical Examiners (NBME) and the Federation of State Medical Boards (FSMB). The USMLE serves as the single examination system domestically and internationally for those seeking medical licensure in the United States.

The Step 1 exam includes test items that can be grouped by the organizational constructs outlined in Table 1 (in order of tested frequency). In late 2020, the NBME increased the number of items assessing communication skills. While pharmacology is still tested, they are focusing on drug mechanisms rather than on pharmacotherapy. You will generally not be required to identify specific medications indicated for a specific condition. Instead, you will be asked more about mechanisms and side effects.

**TABLE 1. Frequency of Various Constructs Tested on the USMLE Step 1.***

| Competency | Range, % | System | Range, % |
|---|---|---|---|
| Medical knowledge: applying foundational science concepts | 60–70 | General principles | 12–16 |
| Patient care: diagnosis | 20–25 | Behavioral health & nervous systems/special senses | 9–13 |
| Communication and interpersonal skills | 6–9 | Respiratory & renal/urinary systems | 9–13 |
| Practice-based learning & improvement | 4–6 | Reproductive & endocrine systems | 9–13 |
| **Discipline** | **Range, %** | Blood & lymphoreticular/immune systems | 7–11 |
| Pathology | 44–52 | Multisystem processes & disorders | 6–10 |
| Physiology | 25–35 | Musculoskeletal, skin & subcutaneous tissue | 6–10 |
| Pharmacology | 15–22 | Cardiovascular system | 5–9 |
| Biochemistry & nutrition | 14–24 | Gastrointestinal system | 5–9 |
| Microbiology | 10–15 | Biostatistics & epidemiology/population health | 4–6 |
| Immunology | 6–11 | Social sciences: communication skills/ethics | 6–9 |
| Gross anatomy & embryology | 11–15 | | |
| Histology & cell biology | 8–13 | | |
| Behavioral sciences | 8–15 | | |
| Genetics | 5–9 | | |

*Percentages are subject to change at any time. www.usmle.org

### How Is the Computer-Based Test (CBT) Structured?

The CBT Step 1 exam consists of one “optional” tutorial/simulation block and seven “real” question blocks of up to 40 questions per block with no more than 280 questions in total, timed at 60 minutes per block. A short 11-question survey follows the last question block. The computer begins the survey with a prompt to proceed to the next block of questions.

Once an examinee finishes a particular question block on the CBT, he or she must click on a screen icon to continue to the next block. Examinees **cannot** go back and change their answers to questions from any previously completed block. However, changing answers is allowed **within** a block of questions as long as the block has not been ended and if time permits.

### What Is the CBT Like?

Given the unique environment of the CBT, it’s important that you become familiar ahead of time with what your test-day conditions will be like. You can access a 15-minute tutorial and practice blocks at http://orientation.nbme.org/Launch/USMLE/STPF1. This tutorial interface is very similar to the one you will use in the exam; learn it now and you can skip taking it during the exam, giving you up to 15 extra minutes of break time. You can gain experience with the CBT format by taking the 120 practice questions (3 blocks with 40 questions each) available online or by signing up for a practice session at a test center for a fee.

For security reasons, examinees are not allowed to bring any personal electronic equipment into the testing area. This includes both digital and analog watches, cell phones, tablets, and calculators. Examinees are also prohibited from carrying in their books, notes, pens/pencils, and scratch paper. Food and beverages are also prohibited in the testing area. The testing centers are monitored by audio and video surveillance equipment. However, most testing centers allot each examinee a small locker outside the testing area in which he or she can store snacks, beverages, and personal items.

- *Keyboard shortcuts:*
  - *A, B, etc—letter choices*
  - *Esc—exit pop-up Calculator and Notes windows*

Questions are typically presented in multiple choice format, with 4–5 possible answer options. There is a countdown timer on the lower left corner of the screen as well. There is also a button that allows the examinee to mark a question for review. If a given question happens to be longer than the screen (which occurs very rarely), a scroll bar will appear on the right, allowing the examinee to see the rest of the question. Regardless of whether the examinee clicks on an answer choice or leaves it blank, he or she must click the "Next" button to advance to the next question.

- *Heart sounds are tested via media questions. Make sure you know how different heart diseases sound on auscultation.*

- *Be sure to test your headphones during the tutorial.*

The USMLE features a small number of media clips in the form of audio and/or video. There may even be a question with a multimedia heart sound simulation. In these questions, a digital image of a torso appears on the screen, and the examinee directs a digital stethoscope to various auscultation points to listen for heart and breath sounds. The USMLE orientation materials include several practice questions in these formats. During the exam tutorial, examinees are given an opportunity to ensure that both the audio headphones and the volume are functioning properly. If you are already familiar with the tutorial and planning on skipping it, first skip ahead to the section where you can test your headphones. After you are sure the headphones are working properly, proceed to the exam.

- *Familiarize yourself with the commonly tested lab values (eg, Hb, WBC, platelets, $Na^+$, $K^+$).*

The examinee can call up a window displaying normal laboratory values. In order to do so, he or she must click the "Lab" icon on the top part of the screen. Afterward, the examinee will have the option to choose between "Blood," "Cerebrospinal," "Hematologic," or "Sweat and Urine." The normal values screen may obscure the question if it is expanded. The examinee may have to scroll down to search for the needed lab values. You might want to memorize some common lab values so you spend less time on questions that require you to analyze these.

- *Illustrations on the test include:*
  - *Gross specimen photos*
  - *Histology slides*
  - *Medical imaging (eg, x-ray, CT, MRI)*
  - *Electron micrographs*
  - *Line drawings*

The CBT interface provides a running list of questions on the left part of the screen at all times. The software also permits examinees to highlight or cross out information by using their mouse. There is a "Notes" icon on the top part of the screen that allows students to write notes to themselves for review at a later time. Finally, the USMLE has recently added new functionality including text magnification and reverse color (white text on black background). Being familiar with these features can save time and may help you better view and organize the information you need to answer a question.

For those who feel they might benefit, the USMLE offers an opportunity to take a simulated test, or "CBT Practice Session" at a Prometric center. Students are eligible to register for this three-and-one-half-hour practice session after they have received their scheduling permit.

*You can take a shortened CBT practice test at a Prometric center.*

The same USMLE Step 1 sample test items (120 questions) available on the USMLE website, www.usmle.org, are used at these sessions. **No new items will be presented.** The practice session is available at a cost of $75 ($155 if taken outside of the US and Canada) and is divided into a short tutorial and three 1-hour blocks of ~40 test items each. Students receive a printed percent-correct score after completing the session. **No explanations of questions are provided.**

You may register for a practice session online at www.usmle.org. A separate scheduling permit is issued for the practice session. Students should allow two weeks for receipt of this permit.

### How Do I Register to Take the Exam?

*The Prometric website will display a calendar with open test dates.*

Prometric test centers offer Step 1 on a year-round basis, except for the first two weeks in January and major holidays. The exam is given every day except Sunday at most centers. Some schools administer the exam on their own campuses. Check with the test center you want to use before making your exam plans.

US students can apply to take Step 1 at the NBME website. This application allows you to select one of 12 overlapping three-month blocks in which to be tested (eg, April–May–June, June–July–August). Choose your three-month eligibility period wisely. If you need to reschedule outside your initial three-month period, you can request a one-time extension of eligibility for the next contiguous three-month period, and pay a rescheduling fee. The application also includes a photo ID form that must be certified by an official at your medical school to verify your enrollment. After the NBME processes your application, it will send you a scheduling permit.

The scheduling permit you receive from the NBME will contain your USMLE identification number, the eligibility period in which you may take the exam, and two additional numbers. The first of these is known as your "scheduling number." You must have this number in order to make your exam appointment with Prometric. The second number is known as the "candidate identification number," or CIN. Examinees must enter their CINs at the Prometric workstation in order to access their exams. However, you will not be allowed to bring your permit into the exam and will be asked to copy your CIN onto your scratch paper. Prometric has no access to the codes. **Make sure to bring a paper or electronic copy of your permit with you to the exam!** Also bring an unexpired, government-issued photo ID that includes your signature (such as a driver's license or passport). Make sure the name on your photo ID exactly matches the name that appears on your scheduling permit.

- *Be familiar with Prometric's policies for cancellation and rescheduling due to COVID-19.*

Once you receive your scheduling permit, you may access the Prometric website or call Prometric's toll-free number to arrange a time to take the exam. You may contact Prometric two weeks before the test date if you want to confirm identification requirements. Be aware that your exam may be canceled because of circumstances related to the COVID-19 pandemic or other unforeseen events. If that were to happen, you should receive an email from Prometric containing notice of the cancellation and instructions on rescheduling. Visit www.prometric.com for updates regarding their COVID-19 cancellation and rescheduling policies.

- *Test scheduling is done on a "first-come, first-served" basis. It's important to schedule an exam date as soon as you receive your scheduling permit.*

Although requests for taking the exam may be completed more than six months before the test date, examinees will not receive their scheduling permits earlier than six months before the eligibility period. The eligibility period is the three-month period you have chosen to take the exam. Most medical students choose the April–June or June–August period. Because exams are scheduled on a "first-come, first-served" basis, it is recommended that you book an exam date on the Prometric website as soon as you receive your permit. Prometric will provide appointment confirmation on a print-out and by email. Be sure to read the latest *USMLE Bulletin of Information* for further details.

### What If I Need to Reschedule the Exam?

You can change your test date and/or center by contacting Prometric at 1-800-MED-EXAM (1-800-633-3926) or www.prometric.com. Make sure to have your CIN when rescheduling. If you are rescheduling by phone, you must speak with a Prometric representative; leaving a voicemail message will not suffice. To avoid a rescheduling fee, you will need to request a change at least 31 calendar days before your appointment. Please note that your rescheduled test date must fall within your assigned three-month eligibility period.

- *Register six months in advance for seating and scheduling preference.*

### When Should I Register for the Exam?

You should plan to register as far in advance as possible ahead of your desired test date (eg, six months), but, depending on your particular test center, new dates and times may open closer to the date. Scheduling early will guarantee that you will get either your test center of choice or one within a 50-mile radius of your first choice. For most US medical students, the desired testing window is in June, since most medical school curricula for the second year end in May or June. Thus, US medical students should plan to register before January in anticipation of a June test date. The timing of the exam is more flexible for IMGs, as it is related only to when they finish exam preparation. Talk with upperclassmen who have already taken the test so you have real-life experience from students who went through a similar curriculum, then formulate your own strategy.

### Where Can I Take the Exam?

Your testing location is arranged with Prometric when you book your test date (after you receive your scheduling permit). For a list of Prometric locations nearest you, visit www.prometric.com.

### How Long Will I Have to Wait Before I Get My Scores?

The USMLE reports scores in three to four weeks, unless there are delays in score processing. Examinees will be notified via email when their scores are available. By following the online instructions, examinees will be able to view, download, and print their score report online for ~120 days after score notification, after which scores can only be obtained through requesting an official USMLE transcript. Additional information about score timetables and accessibility is available on the official USMLE website.

### What About Time?

Time is of special interest on the CBT exam. Here's a breakdown of the exam schedule:

| | |
|---|---|
| 15 minutes | Tutorial (skip if familiar with test format and features) |
| 7 hours | Seven 60-minute question blocks |
| 45 minutes | Break time (includes time for lunch) |

The computer will keep track of how much time has elapsed on the exam. However, the computer will show you only how much time you have remaining in a given block. Therefore, it is up to you to determine if you are pacing yourself properly (at a rate of approximately one question per 90 seconds).

The computer does not warn you if you are spending more than your allotted time for a break. You should therefore budget your time so that you can take a short break when you need one and have time to eat. You must be especially careful not to spend too much time in between blocks (you should keep track of how much time elapses from the time you finish a block of questions to the time you start the next block). After you finish one question block, you'll need to click to proceed to the next block of questions. If you do not click within 30 seconds, you will automatically be entered into a break period.

Break time for the day is 45 minutes, but you are not required to use all of it, nor are you required to use any of it. You can gain extra break time (but not extra time for the question blocks) by skipping the tutorial or by finishing a block ahead of the allotted time. Any time remaining on the clock when you finish a block gets added to your remaining break time. Once a new question block has been started, you may not take a break until you have reached the end of that block. If you do so, this will be recorded as an "unauthorized break" and will be reported on your final score report.

Finally, be aware that it may take a few minutes of your break time to "check out" of the secure resting room and then "check in" again to resume testing, so plan accordingly. The "check-in" process may include fingerprints, pocket checks, and metal detector scanning. Some students recommend pocketless clothing on exam day to streamline the process.

- *Gain extra break time by skipping the tutorial, or utilize the tutorial time to add personal notes to your scratch paper.*

- *Be careful to watch the clock on your break time.*

### If I Freak Out and Leave, What Happens to My Score?

Your scheduling permit shows a CIN that you will need to enter to start your exam. Entering the CIN is the same as breaking the seal on a test book, and you are considered to have started the exam when you do so. However, no score will be reported if you do not complete the exam. In fact, if you leave at any time from the start of the test to the last block, no score will be reported. The fact that you started but did not complete the exam, however, will appear on your USMLE score transcript. Even though a score is not posted for incomplete tests, examinees may still get an option to request that their scores be calculated and reported if they desire; unanswered questions will be scored as incorrect.

The exam ends when all question blocks have been completed or when their time has expired. As you leave the testing center, you will receive a printed test-completion notice to document your completion of the exam. To receive an official score, you must finish the entire exam.

### What Types of Questions Are Asked?

> *Nearly three fourths of Step 1 questions begin with a description of a patient.*

All questions on the exam are **one-best-answer multiple choice items.** Most questions consist of a clinical scenario or a direct question followed by a list of five or more options. You are required to select the single best answer among the options given. There are no "except," "not," or matching questions on the exam. A number of options may be partially correct, in which case you must select the option that best answers the question or completes the statement. Additionally, keep in mind that experimental questions may appear on the exam, which do not affect your score.

### How Is the Test Scored?

> *Determine if the impending transition to Pass/Fail scoring impacts your optimal testing date.*

**The USMLE will be transitioning to a Pass/Fail scoring system no earlier than January 1, 2022.** Results from Step 1 exams taken prior to the transition date will be reported using a three-digit test score. Changes will not be made to transcripts containing a three-digit test score after the switch to Pass/Fail grading. Should you consider delaying your exam until Pass/Fail scoring is implemented? At the moment, we don't think so in most situations. First, at press time, the actual implementation date has not been announced. Second, and more importantly, the test date should be driven by your readiness relative to your curriculum and school schedule. On the other hand, there are a number of possible reasons that you might want to consider taking your exam in 2021 and getting a 3-digit score. These may include interest in a competitive specialty, IMG status, and enrollment at a less competitive medical school. In these situations, the USMLE Step 2 CK can provide an additional opportunity to score well and demonstrate a strong fund of knowledge. Consult with your school advisors and follow us on social media for timely updates.

Examinees taking the current test will receive an electronic report that includes the examinee's pass/fail status, a three-digit test score, a bar chart comparing the examinee's performance to that of other examinees', and a

graphic depiction of the examinee's performance by physician task, discipline and organ system.

The USMLE score report (see Figure 1) highlights the examinee's strength and weaknesses by providing an overview of their performance by physician task, discipline and organ system compared to their overall performance on the exam. Each of the questions (minus experimental questions) is tagged according to any or all relevant content areas. Yellow-colored boxes (lower, same, higher) on your score report indicate your performance in each specific content area **relative to your overall performance** on the exam.

The NBME provides a three-digit test score based on the total number of items answered correctly on the examination, which corresponds to a particular percentile (see Figure 2). Your three-digit score will be qualified by the mean and standard deviation of US and Canadian medical school first-time examinees.

Since some questions may be experimental and are not counted, it is possible to get different scores for the same number of correct answers. In 2018, the mean score was 231 with a standard deviation of 19.

The passing score for Step 1 is 194. The NBME does not report the minimum number of correct responses needed to pass, but estimates that it is roughly 60–70%. The NBME may adjust the minimum passing score in the future, so please check the USMLE website or www.firstaidteam.com for updates.

- *The mean Step 1 score for US medical students continues to rise, from 200 in 1991 to 231 in 2018.*

**FIGURE 1. Samples from the USMLE Step 1 Performance Profile.**

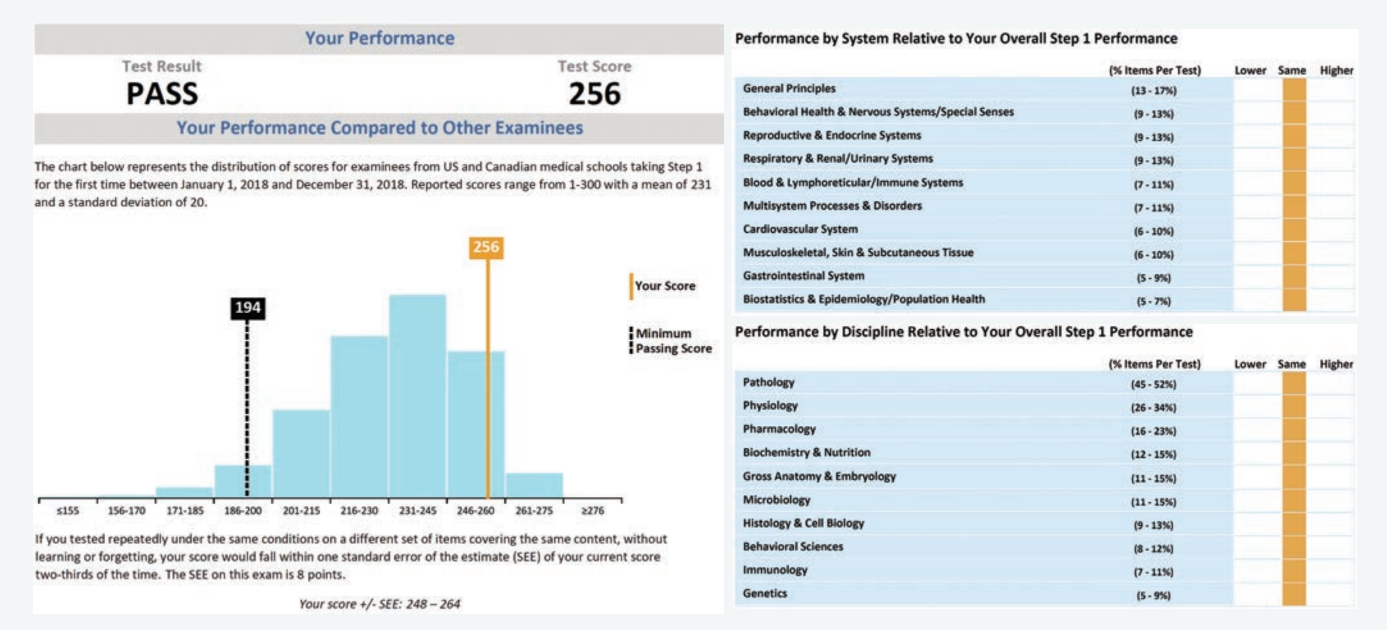
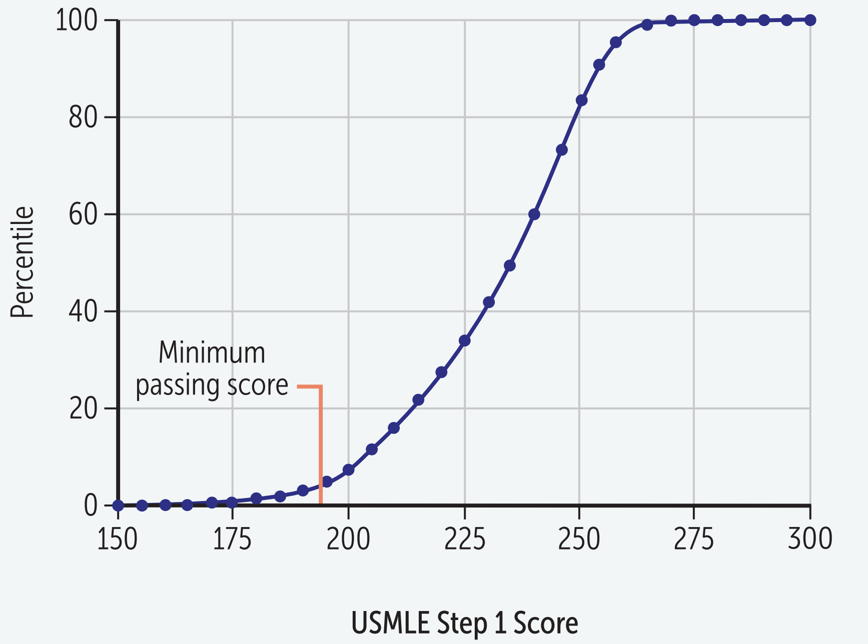


**FIGURE 2. Score and Percentile for First-time Step 1 Takers.**




N=72,473 including US and Canadian medical school students testing between January 1, 2016–December 31, 2018. www.usmle.org.

According to the USMLE, medical schools receive a listing of total scores and pass/fail results plus group summaries by discipline and organ system. Students can withhold their scores from their medical school if they wish. Official USMLE transcripts, which can be sent on request to residency programs, include only total scores, not performance profiles.

Consult the USMLE website or your medical school for the most current and accurate information regarding the examination.

**TABLE 2. Passing Rates for the 2018–2019 USMLE Step 1.**[2]

| | 2018 | | 2019 | |
|---|---|---|---|---|
| | No. Tested | % Passing | No. Tested | % Passing |
| Allopathic 1st takers | 20,670 | 96% | 21,308 | 97% |
| Repeaters | 941 | 67% | 838 | 66% |
| Allopathic total | 21,611 | 95% | 22,146 | 96% |
| Osteopathic 1st takers | 4,092 | 96% | 4,794 | 96% |
| Repeaters | 44 | 73% | 43 | 67% |
| Osteopathic total | 4,136 | 96% | 4,837 | 96% |
| **Total US/Canadian** | **25,747** | **94%** | **26,983** | **96%** |
| IMG 1st takers | 14,332 | 80% | 14,046 | 82% |
| Repeaters | 2,111 | 44% | 2,019 | 45% |
| IMG total | **16,443** | 75% | **16,065** | 78% |
| **Total Step 1 examinees** | **42,190** | 87% | **43,048** | 89% |

### What Does My Score Mean?

The most important point with the Step 1 score, while they still report it, is passing versus failing. Passing essentially means, "Hey, you're on your way to becoming a fully licensed doc." As Table 2 shows, the majority of students pass the exam, so remember, we told you to relax.

Beyond that, the main point of having a quantitative score is to give you a sense of how well you've done on the exam and to help schools and residencies rank their students and applicants, respectively.

### Official NBME/USMLE Resources

The NBME offers a Comprehensive Basic Science Examination (CBSE) for practice that is a shorter version of the Step 1. The CBSE contains four blocks of 50 questions each and covers material that is typically learned during the basic science years. Scores range from 45 to 95 and correlate with a Step 1 equivalent (see Table 3). The standard error of measurement is approximately 3 points, meaning a score of 80 would estimate the student's proficiency is somewhere between 77 and 83. In other words, the actual Step 1 score could be predicted to be between 218 and 232. Of course, these values do not correlate exactly, and they do not reflect different test preparation methods. Many schools use this test to gauge whether a student is expected to pass Step 1. If this test is offered by your school, it is usually conducted at the end of regular didactic time before any dedicated Step 1 preparation. If you do not encounter the CBSE before your dedicated study time, you need not worry about taking it. Use the information to help set realistic goals and timetables for your success.

The NBME also offers six forms of Comprehensive Basic Science Self-Assessment (CBSSA). Students who prepared for the exam using this web-based tool reported that they found the format and content highly indicative of questions tested on the actual exam. In addition, the CBSSA is a fair predictor of USMLE performance (see Table 4). The test interface, however, does not match the actual USMLE test interface, so practicing with these forms alone is not advised.

The CBSSA exists in two formats: standard-paced and self-paced, both of which consist of four sections of 50 questions each (for a total of 200 multiple choice items). The standard-paced format allows the user up to 75 minutes to complete each section, reflecting time limits similar to the actual exam. By contrast, the self-paced format places a 5-hour time limit on answering all multiple choice questions. Every few years, a new form is released and an older one is retired, reflecting changes in exam content. Therefore, the newer exams tend to be more similar to the actual Step 1, and scores from these exams tend to provide a better estimation of exam day performance.

Keep in mind that this bank of questions is available only on the web. The NBME requires that users start and complete the exam within 90 days of purchase. Once the assessment has begun, users are required to complete the sections within 20 days. Following completion of the questions, the

- *Practice questions may be easier than the actual exam.*

**TABLE 3. CBSE to USMLE Score Prediction.**

| CBSE Score | Step 1 Equivalent |
|---|---|
| ≥ 94 | ≥ 260 |
| 92 | 255 |
| 90 | 250 |
| 88 | 245 |
| 86 | 240 |
| 84 | 235 |
| 82 | 230 |
| 80 | 225 |
| 78 | 220 |
| 76 | 215 |
| 74 | 210 |
| 72 | 205 |
| 70 | 200 |
| 68 | 195 |
| 66 | 190 |
| 64 | 185 |
| 62 | 180 |
| 60 | 175 |
| 58 | 170 |
| 56 | 165 |
| 54 | 160 |
| 52 | 155 |
| 50 | 150 |
| 48 | 145 |
| 46 | 140 |
| ≤ 44 | ≤ 135 |

**TABLE 4. CBSSA to USMLE Score Prediction.**

| CBSSA Score | Approximate USMLE Step 1 Score |
|---|---|
| 150 | 155 |
| 200 | 165 |
| 250 | 175 |
| 300 | 186 |
| 350 | 196 |
| 400 | 207 |
| 450 | 217 |
| 500 | 228 |
| 550 | 238 |
| 600 | 248 |
| 650 | 259 |
| 700 | 269 |
| 750 | 280 |
| 800 | 290 |

CBSSA provides a performance profile indicating the user's relative strengths and weaknesses, much like the report profile for the USMLE Step 1 exam. The profile is scaled with an average score of 500 and a standard deviation of 100. In addition to the performance profile, examinees will be informed of the number of questions answered incorrectly. You will have the ability to review the text of the incorrect question with the correct answer. Explanations for the correct answer, however, will not be provided. The NBME charges $60 for assessments with expanded feedback. The fees are payable by credit card or money order. For more information regarding the CBSE and the CBSSA, visit the NBME's website at www.nbme.org.

The NBME scoring system is weighted for each assessment exam. While some exams seem more difficult than others, the score reported takes into account these inter-test differences when predicting Step 1 performance. Also, while many students report seeing Step 1 questions "word-for-word" out of the assessments, the NBME makes special note that no live USMLE questions are shown on any NBME assessment.

Lastly, the International Foundations of Medicine (IFOM) offers a Basic Science Examination (BSE) practice exam at participating Prometric test centers for $200. Students may also take the self-assessment test online for $35 through the NBME's website. The IFOM BSE is intended to determine an examinee's relative areas of strength and weakness in general areas of basic science—not to predict performance on the USMLE Step 1 exam—and the content covered by the two examinations is somewhat different. However, because there is substantial overlap in content coverage and many IFOM items were previously used on the USMLE Step 1, it is possible to roughly project IFOM performance onto the USMLE Step 1 score scale. More information is available at http://www.nbme.org/ifom/.

## ▸ DEFINING YOUR GOAL

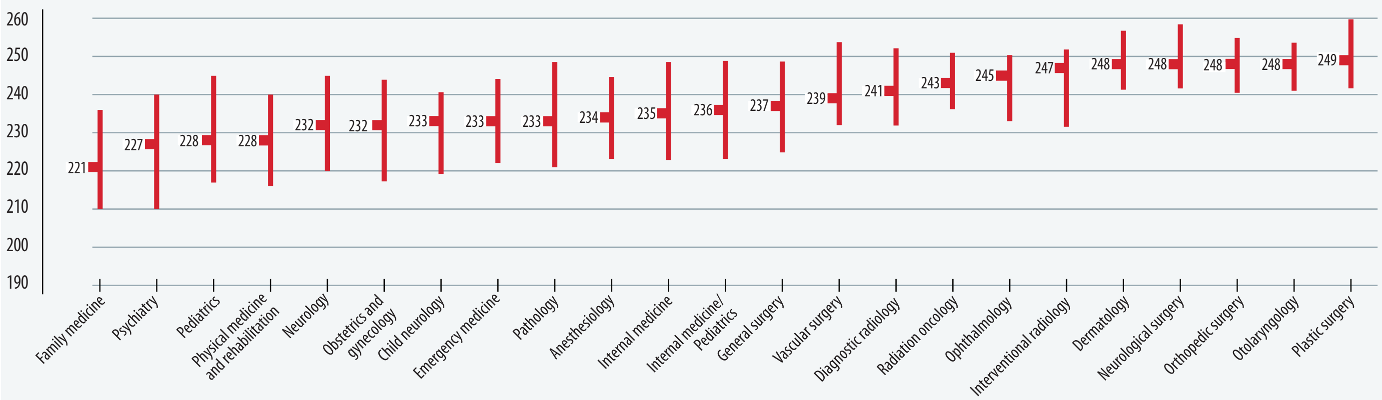
> ▸ *Some competitive residency programs place more weight on Step 1 scores when choosing candidates to interview.*

> ▸ *Fourth-year medical students have the best feel for how Step 1 scores factor into the residency application process.*

It is useful to define your own personal performance goal when approaching the USMLE Step 1. Your style and intensity of preparation can then be matched to your goal. Furthermore, your goal may depend on your school's requirements, your specialty choice, your grades to date, and your personal assessment of the test's importance. Do your best to define your goals early so that you can prepare accordingly.

The value of the USMLE Step 1 score in selecting residency applicants remains controversial, and some have called for less emphasis to be placed on the score when selecting or screening applicants.[3] For the time being, however, it continues to be an important part of the residency application, and it is not uncommon for some specialties to implement filters that screen out applicants who score below a certain cutoff. This is more likely to be seen in competitive specialties (eg, orthopedic surgery, ophthalmology, dermatology, otolaryngology). Independent of your career goals, you can maximize your future options by doing your best to obtain the highest score possible (see Figure 3). At the same time, your Step 1 score is only one of a number of

**FIGURE 3. Median USMLE Step 1 Score by Specialty for Matched US Seniors.**[a,b]




[a]Vertical lines show interquartile range.
[b]Data from National Resident Matching Program. Charting outcomes in the match. https://mk0nrmp3oyqui6wqfm.kinstacdn.com/wp-content/uploads/2020/07/Charting-Outcomes-in-the-Match-2020_MD-Senior_final.pdf. Published July 2020.

factors that are assessed when you apply for residency. In fact, many residency programs value other criteria such as letters of recommendation, third-year clerkship grades, honors, and research experience more than a high score on Step 1. Fourth-year medical students who have recently completed the residency application process can be a valuable resource in this regard.

## LEARNING STRATEGIES

Many students feel overwhelmed during the preclinical years and struggle to find an effective learning strategy. Table 5 lists several learning strategies you can try and their estimated effectiveness for Step 1 preparation based on the literature (see References). These are merely suggestions, and it's important to take your learning preferences into account. Your comprehensive learning approach will contain a combination of strategies (eg, elaborative interrogation followed by practice testing, mnemonics review using spaced repetition, etc). Regardless of your choice, the foundation of knowledge you build during your basic science years is the most important resource for success on the USMLE Step 1.

> *The foundation of knowledge you build during your basic science years is the most important resource for success on the USMLE Step 1.*

### HIGH EFFICACY

#### Practice Testing

Also called "retrieval practice," practice testing has both direct and indirect benefits to the learner.[4] Effortful retrieval of answers does not only identify weak spots—it directly strengthens long-term retention of material.[5] The more effortful the recall, the better the long-term retention. This advantage has been shown to result in higher test scores and GPAs.[6] In fact, research has shown a positive correlation between the number of boards-style practice questions completed and Step 1 scores among medical students.[7]

> *Research has shown a positive correlation between the number of boards-style practice questions completed and Step 1 scores among medical students.*

**TABLE 5. Effective Learning Strategies.**

| EFFICACY | STRATEGY | EXAMPLE RESOURCES |
|---|---|---|
| *High efficacy* | Practice testing (retrieval practice) | UWorld Qbank<br>NBME Self-Assessments<br>USMLE-Rx QMax<br>Kaplan Qbank |
| | Distributed practice | USMLE-Rx Flash Facts<br>Anki<br>Firecracker<br>Memorang<br>Osmosis |
| *Moderate efficacy* | Mnemonics | *Pre-made:*<br>SketchyMedical<br>Picmonic<br>*Self-made:*<br>Mullen Memory |
| | Elaborative interrogation/ self-explanation | |
| | Concept mapping | Coggle<br>FreeMind<br>XMind<br>MindNode |
| *Low efficacy* | Rereading | |
| | Highlighting/underlining | |
| | Summarization | |

Practice testing should be done with "interleaving" (mixing of questions from different topics in a single session). Question banks often allow you to intermingle topics. Interleaved practice helps learners develop their ability to focus on the relevant concept when faced with many possibilities. Practicing topics in massed fashion (eg, all cardiology, then all dermatology) may seem intuitive, but there is strong evidence that interleaving correlates with longer-term retention and increased student achievement, especially on tasks that involve problem solving.[5]

In addition to using question banks, you can test yourself by arranging your notes in a question-answer format (eg, via flash cards). Testing these Q&As in random order allows you to reap the benefit of interleaved practice. Bear in mind that the utility of practice testing comes from the practice of information retrieval, so simply reading through Q&As will attenuate this benefit.

### Distributed Practice

Also called "spaced repetition," distributed practice is the opposite of massed practice or "cramming." Learners review material at increasingly spaced out

intervals (days to weeks to months). Massed learning may produce more short-term gains and satisfaction, but learners who use distributed practice have better mastery and retention over the long term.[5,9]

Flash cards are a simple way to incorporate both distributed practice and practice testing. Studies have linked spaced repetition learning with flash cards to improved long-term knowledge retention and higher exam scores.[6,8,10] Apps with automated spaced-repetition software (SRS) for flash cards exist for smartphones and tablets, so the cards are accessible anywhere. Proceed with caution: there is an art to making and reviewing cards. The ease of quickly downloading or creating digital cards can lead to flash card overload (it is unsustainable to make 50 flash cards per lecture!). Even at a modest pace, the thousands upon thousands of cards are too overwhelming for Step 1 preparation. Unless you have specific high-yield cards (and have checked the content with high-yield resources), stick to pre-made cards by reputable sources that curate the vast amount of knowledge for you.

▶ *Studies have linked spaced repetition learning with flash cards to improved long-term knowledge retention and higher exam scores.*

If you prefer pen and paper, consider using a planner or spreadsheet to organize your study material over time. Distributed practice allows for some forgetting of information, and the added effort of recall over time strengthens the learning.

## MODERATE EFFICACY

### Mnemonics

A "mnemonic" refers to any device that assists memory, such as acronyms, mental imagery (eg, keywords with or without memory palaces), etc. Keyword mnemonics have been shown to produce superior knowledge retention when compared with rote memorization in many scenarios. However, they are generally more effective when applied to memorization-heavy, keyword-friendly topics and may not be broadly suitable.[5] Keyword mnemonics may not produce long-term retention, so consider combining mnemonics with distributed, retrieval-based practice (eg, via flash cards with SRS).

Self-made mnemonics may have an advantage when material is simple and keyword friendly. If you can create your own mnemonic that accurately represents the material, this will be more memorable. When topics are complex and accurate mnemonics are challenging to create, pre-made mnemonics may be more effective, especially if you are inexperienced at creating mnemonics.[11]

### Elaborative Interrogation/Self-Explanation

Elaborative interrogation ("why" questions) and self-explanation (general questioning) prompt learners to generate explanations for facts. When reading passages of discrete facts, consider using these techniques, which have been shown to be more effective than rereading (eg, improved recall and better problem-solving/diagnostic performance).[5,12,13]

▶ *Elaborative interrogation and self-explanation prompt learners to generate explanations for facts, which improves recall and problem solving.*

### Concept Mapping

Concept mapping is a method for graphically organizing knowledge, with concepts enclosed in boxes and lines drawn between related concepts. Creating or studying concept maps may be more effective than other activities (eg, writing or reading summaries/outlines). However, studies have reached mixed conclusions about its utility, and the small size of this effect raises doubts about its authenticity and pedagogic significance.[14]

## LOW EFFICACY

### Rereading

While the most commonly used method among surveyed students, rereading has not been shown to correlate with grade point average.[9] Due to its popularity, rereading is often a comparator in studies on learning. Other strategies that we have discussed (eg, practice testing) have been shown to be significantly more effective than rereading.

### Highlighting/Underlining

Because this method is passive, it tends to be of minimal value for learning and recall. In fact, lower-performing students are more likely to use these techniques.[9] Students who highlight and underline do not learn how to actively recall learned information and thus find it difficult to apply knowledge to exam questions.

### Summarization

While more useful for improving performance on generative measures (eg, free recall or essays), summarization is less useful for exams that depend on recognition (eg, multiple choice). Findings on the overall efficacy of this method have been mixed.[5]

## ▶ TIMELINE FOR STUDY

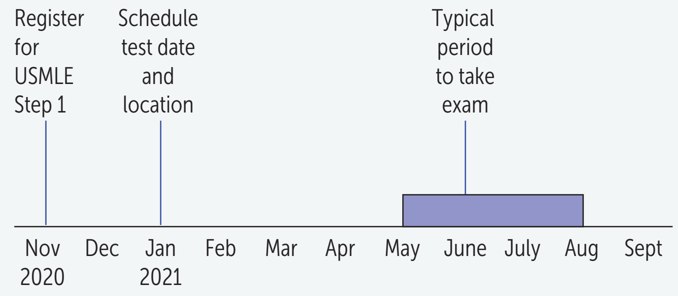
### Before Starting

Your preparation for the USMLE Step 1 should begin when you enter medical school. Organize and commit to studying from the beginning so that when the time comes to prepare for the USMLE, you will be ready with a strong foundation.

### Make a Schedule

After you have defined your goals, map out a study schedule that is consistent with your objectives, your vacation time, the difficulty of your ongoing

**FIGURE 4. Typical Timeline for the USMLE Step 1.**




▶ *Customize your schedule. Tackle your weakest section first.*

coursework, and your family and social commitments (see Figure 4). Determine whether you want to spread out your study time or concentrate it into 14-hour study days in the final weeks. Then factor in your own history in preparing for standardized examinations (eg, SAT, MCAT). Talk to students at your school who have recently taken Step 1. Ask them for their study schedules, especially those who have study habits and goals similar to yours. Sample schedules can be found at https://firstaidteam.com/schedules/.

Typically, US medical schools allot between four and eight weeks for dedicated Step 1 preparation. The time you dedicate to exam preparation will depend on your target score as well as your success in preparing yourself during the first two years of medical school. Some students reserve about a week at the end of their study period for final review; others save just a few days. When you have scheduled your exam date, do your best to adhere to it. Studies show that a later testing date does not translate into a higher score, so avoid pushing back your test date without good reason.[15]

Make your schedule realistic, and set achievable goals. Many students make the mistake of studying at a level of detail that requires too much time for a comprehensive review—reading *Gray's Anatomy* in a couple of days is not a realistic goal! Have one catch-up day per week of studying. No matter how well you stick to your schedule, unexpected events happen. But don't let yourself procrastinate because you have catch-up days; stick to your schedule as closely as possible and revise it regularly on the basis of your actual progress. Be careful not to lose focus. Beware of feelings of inadequacy when comparing study schedules and progress with your peers. **Avoid others who stress you out.** Focus on a few top-rated resources that suit your learning style—not on some obscure books your friends may pass down to you. Accept the fact that you cannot learn it all.

▶ *Avoid burnout. Maintain proper diet, exercise, and sleep habits.*

You will need time for uninterrupted and focused study. Plan your personal affairs to minimize crisis situations near the date of the test. Allot an adequate number of breaks in your study schedule to avoid burnout. Maintain a healthy lifestyle with proper diet, exercise, and sleep.

Another important aspect of your preparation is your studying environment. **Study where you have always been comfortable studying.** Be sure to include everything you need close by (review books, notes, coffee, snacks,

etc). If you're the kind of person who cannot study alone, form a study group with other students taking the exam. The main point here is to create a comfortable environment with minimal distractions.

### Year(s) Prior

The knowledge you gained during your first two years of medical school and even during your undergraduate years should provide the groundwork on which to base your test preparation. Student scores on NBME subject tests (commonly known as "shelf exams") have been shown to be highly correlated with subsequent Step 1 scores.[16] Moreover, undergraduate science GPAs as well as MCAT scores are strong predictors of performance on the Step 1 exam.[17]

▶ *Buy review books early (first year) and use while studying for courses.*

We also recommend that you buy highly rated review books early in your first year of medical school and use them as you study throughout the two years. When Step 1 comes along, these books will be familiar and personalized to the way in which you learn. It is risky and intimidating to use unfamiliar review books in the final two or three weeks preceding the exam. Some students find it helpful to personalize and annotate *First Aid* throughout the curriculum.

### Months Prior

Review test dates and the application procedure. Testing for the USMLE Step 1 is done on a year-round basis. If you have disabilities or special circumstances, contact the NBME as early as possible to discuss test accommodations (see the Section I Supplement at www.firstaidteam.com/bonus).

▶ *Simulate the USMLE Step 1 under "real" conditions before beginning your studies.*

Use this time to finalize your ideal schedule. Consider upcoming breaks and whether you want to relax or study. Work backward from your test date to make sure you finish at least one question bank. Also add time to redo missed or flagged questions (which may be half the bank). This is the time to build a structured plan with enough flexibility for the realities of life.

Begin doing blocks of questions from reputable question banks under "real" conditions. Don't use tutor mode until you're sure you can finish blocks in the allotted time. It is important to continue balancing success in your normal studies with the Step 1 test preparation process.

### Weeks Prior (Dedicated Preparation)

Your dedicated prep time may be one week or two months. You should have a working plan as you go into this period. Finish your schoolwork strong, take a day off, and then get to work. Start by simulating a full-length USMLE Step 1 if you haven't yet done so. Consider doing one NBME CBSSA and the free questions from the NBME website. Alternatively, you could choose 7 blocks of randomized questions from a commercial question bank. Make sure you get feedback on your strengths and weaknesses and adjust your studying

accordingly. Many students study from review sources or comprehensive programs for part of the day, then do question blocks. Also, keep in mind that reviewing a question block can take upward of two hours. Feedback from CBSSA exams and question banks will help you focus on your weaknesses.

- *In the final two weeks, focus on review, practice questions, and endurance. Stay confident!*

### One Week Prior

Make sure you have your CIN (found on your scheduling permit) as well as other items necessary for the day of the examination, including a current driver's license or another form of photo ID with your signature (make sure the name on your **ID exactly** matches that on your scheduling permit). Confirm the Prometric testing center location and test time. Work out how you will get to the testing center and what parking and traffic problems you might encounter. Drive separately from other students taking the test on the same day, and exchange cell phone numbers in case of emergencies. If possible, visit the testing site to get a better idea of the testing conditions you will face. Determine what you will do for lunch. Make sure you have everything you need to ensure that you will be comfortable and alert at the test site. It may be beneficial to adjust your schedule to start waking up at the same time that you will on your test day. And of course, make sure to maintain a healthy lifestyle and get enough sleep.

- *One week before the test:*
  - *Sleep according to the same schedule you'll use on test day*
  - *Review the CBT tutorial one last time*
  - *Call Prometric to confirm test date and time*

### One Day Prior

Try your best to relax and rest the night before the test. Double-check your admissions and test-taking materials as well as the comfort measures discussed earlier so that you will not have to deal with such details on the morning of the exam. At this point it will be more effective to review short-term memory material that you're already familiar with than to try to learn new material. The Rapid Review section at the end of this book is high yield for last-minute studying. Remember that regardless of how hard you have studied, you cannot know everything. There will be things on the exam that you have never even seen before, so do not panic. Do not underestimate your abilities.

Many students report difficulty sleeping the night prior to the exam. This is often exacerbated by going to bed much earlier than usual. Do whatever it takes to ensure a good night's sleep (eg, massage, exercise, warm milk, no back-lit screens at night). Do not change your daily routine prior to the exam. Exam day is not the day for a caffeine-withdrawal headache.

### Morning of the Exam

- *No notes, books, calculators, pagers, cell phones, recording devices, or watches of any kind are allowed in the testing area, but they are allowed in lockers.*

On the morning of the Step 1 exam, wake up at your regular time and eat a normal breakfast. If you think it will help you, have a close friend or family member check to make sure you get out of bed. Make sure you have your scheduling permit admission ticket, test-taking materials, and comfort measures as discussed earlier. Wear loose, comfortable clothing. Plan for a variable temperature in the testing center. Arrive at the test site 30 minutes

*Arrive at the testing center 30 minutes before your scheduled exam time. If you arrive more than half an hour late, you will not be allowed to take the test.*

before the time designated on the admission ticket; however, do not come too early, as doing so may intensify your anxiety. When you arrive at the test site, the proctor should give you a USMLE information sheet that will explain critical factors such as the proper use of break time. Seating may be assigned, but ask to be reseated if necessary; you need to be seated in an area that will allow you to remain comfortable and to concentrate. Get to know your testing station, especially if you have never been in a Prometric testing center before. Listen to your proctors regarding any changes in instructions or testing procedures that may apply to your test site.

Finally, remember that it is natural (and even beneficial) to be a little nervous. Focus on being mentally clear and alert. Avoid panic. When you are asked to begin the exam, take a deep breath, focus on the screen, and then begin. Keep an eye on the timer. Take advantage of breaks between blocks to stretch, maybe do some jumping jacks, and relax for a moment with deep breathing or stretching.

### After the Test

After you have completed the exam, be sure to have fun and relax regardless of how you may feel. Taking the test is an achievement in itself. Remember, you are much more likely to have passed than not. Enjoy the free time you have before your clerkships. Expect to experience some "reentry" phenomena as you try to regain a real life. Once you have recovered sufficiently from the test (or from partying), we invite you to send us your feedback, corrections, and suggestions for entries, facts, mnemonics, strategies, resource ratings, and the like (see p. xvii, How to Contribute). Sharing your experience will benefit fellow medical students.

## STUDY MATERIALS

### Quality Considerations

Although an ever-increasing number of review books and software are now available on the market, the quality of such material is highly variable. Some common problems are as follows:

- Certain review books are too detailed to allow for review in a reasonable amount of time or cover subtopics that are not emphasized on the exam.
- Many sample question books were originally written years ago and have not been adequately updated to reflect recent trends.
- Some question banks test to a level of detail that you will not find on the exam.

*If a given review book is not working for you, stop using it no matter how highly rated it may be or how much it costs.*

### Review Books

In selecting review books, be sure to weigh different opinions against each other, read the reviews and ratings in Section IV of this guide, examine the

books closely in the bookstore, and choose carefully. You are investing not only money but also your limited study time. Do not worry about finding the "perfect" book, as many subjects simply do not have one, and different students prefer different formats. Supplement your chosen books with personal notes from other sources, including what you learn from question banks.

There are two types of review books: those that are stand-alone titles and those that are part of a series. Books in a series generally have the same style, and you must decide if that style works for you. However, a given style is not optimal for every subject.

- *Charts and diagrams may be the best approach for physiology and biochemistry, whereas tables and outlines may be preferable for microbiology.*

You should also find out which books are up to date. Some recent editions reflect major improvements, whereas others contain only cursory changes. Take into consideration how a book reflects the format of the USMLE Step 1.

### Apps

With the explosion of smartphones and tablets, apps are an increasingly popular way to review for the Step 1 exam. The majority of apps are compatible with both iOS and Android. Many popular Step 1 review resources (eg, UWorld, USMLE-Rx) have apps that are compatible with their software. Many popular web references (eg, UpToDate) also now offer app versions. All of these apps offer flexibility, allowing you to study while away from a computer (eg, while traveling).

### Practice Tests

Taking practice tests provides valuable information about potential strengths and weaknesses in your fund of knowledge and test-taking skills. Some students use practice examinations simply as a means of breaking up the monotony of studying and adding variety to their study schedule, whereas other students rely almost solely on practice. You should also subscribe to one or more high-quality question banks.

- *Most practice exams are shorter and less clinical than the real thing.*

Additionally, some students preparing for the Step 1 exam have started to incorporate case-based books intended primarily for clinical students on the wards or studying for the Step 2 CK exam. *First Aid Cases for the USMLE Step 1* aims to directly address this need.

After taking a practice test, spend time on each question and each answer choice whether you were right or wrong. There are important teaching points in each explanation. Knowing why a wrong answer choice is incorrect is just as important as knowing why the right answer is correct. Do not panic if your practice scores are low as many questions try to trick or distract you to highlight a certain point. Use the questions you missed or were unsure about to develop focused plans during your scheduled catch-up time.

- *Use practice tests to identify concepts and areas of weakness, not just facts that you missed.*

### Textbooks and Course Syllabi

Limit your use of textbooks and course syllabi for Step 1 review. Many textbooks are too detailed for high-yield review and include material that is generally not tested on the USMLE Step 1 (eg, drug dosages, complex chemical structures). Syllabi, although familiar, are inconsistent across medical schools and frequently reflect the emphasis of individual faculty, which often does not correspond to that of the USMLE Step 1. Syllabi also tend to be less organized than top-rated books and generally contain fewer diagrams and study questions.

## ▸ TEST-TAKING STRATEGIES

▸ *Practice! Develop your test-taking skills and strategies well before the test date.*

Your test performance will be influenced by both your knowledge and your test-taking skills. You can strengthen your performance by considering each of these factors. Test-taking skills and strategies should be developed and perfected well in advance of the test date so that you can concentrate on the test itself. We suggest that you try the following strategies to see if they might work for you.

### Pacing

You have seven hours to complete up to 280 questions. Note that each one-hour block contains up to 40 questions. This works out to approximately 90 seconds per question. We recommend following the "1 minute rule" to pace yourself. Spend no more than 1 minute on each question. If you are still unsure about the answer after this time, mark the question, make an educated guess, and move on. Following this rule, you should have approximately 20 minutes left after all questions are answered, which you can use to revisit all of your marked questions. Remember that some questions may be experimental and do not count for points (and reassure yourself that these experimental questions are the ones that are stumping you). In the past, pacing errors have been detrimental to the performance of even highly prepared examinees. The bottom line is to keep one eye on the clock at all times!

▸ *Time management is an important skill for exam success.*

### Dealing with Each Question

There are several established techniques for efficiently approaching multiple choice questions; find what works for you. One technique begins with identifying each question as easy, workable, or impossible. Your goal should be to answer all easy questions, resolve all workable questions in a reasonable amount of time, and make quick and intelligent guesses on all impossible questions. Most students read the stem, think of the answer, and turn immediately to the choices. A second technique is to first skim the answer choices to get a context, then read the last sentence of the question

(the lead-in), and then read through the passage quickly, extracting only information relevant to answering the question. This can be particularly helpful for questions with long clinical vignettes. Try a variety of techniques on practice exams and see what works best for you. If you get overwhelmed, remember that a 30-second time out to refocus may get you back on track.

### Guessing

There is **no penalty** for wrong answers. Thus, **no test block should be left with unanswered questions.** If you don't know the answer, first eliminate incorrect choices, then guess among the remaining options. **Note that dozens of questions are unscored experimental questions** meant to obtain statistics for future exams. Therefore, some questions will seem impossible simply because they are part of the development process for future exams.

### Changing Your Answer

The conventional wisdom is not to change answers that you have already marked unless there is a convincing and logical reason to do so—in other words, go with your "first hunch." Many question banks tell you how many questions you changed from right to wrong, wrong to wrong, and wrong to right. Use this feedback to judge how good a second-guesser you are. If you have extra time, reread the question stem and make sure you didn't misinterpret the question.

▶ *Go with your first hunch, unless you are certain that you are a good second-guesser.*

## ▶ CLINICAL VIGNETTE STRATEGIES

In recent years, the USMLE Step 1 has become increasingly clinically oriented. This change mirrors the trend in medical education toward introducing students to clinical problem solving during the basic science years. The increasing clinical emphasis on Step 1 may be challenging to those students who attend schools with a more traditional curriculum.

▶ *Be prepared to read fast and think on your feet!*

### What Is a Clinical Vignette?

A clinical vignette is a short (usually paragraph-long) description of a patient, including demographics, presenting symptoms, signs, and other information concerning the patient. Sometimes this paragraph is followed by a brief listing of important physical findings and/or laboratory results. The task of assimilating all this information and answering the associated question in the span of one minute can be intimidating. So be prepared to read quickly and think on your feet. Remember that the question is often indirectly asking something you already know.

▶ *Practice questions that include case histories or descriptive vignettes are critical for Step 1 preparation.*

### Strategy

Remember that Step 1 vignettes usually describe diseases or disorders in their most classic presentation. So look for cardinal signs (eg, malar rash for SLE or nuchal rigidity for meningitis) in the narrative history. Be aware that the question will contain classic signs and symptoms instead of buzzwords. Sometimes the data from labs and the physical exam will help you confirm or reject possible diagnoses, thereby helping you rule answer choices in or out. In some cases, they will be a dead giveaway for the diagnosis.

*Step 1 vignettes usually describe diseases or disorders in their most classic presentation.*

Making a diagnosis from the history and data is often not the final answer. Not infrequently, the diagnosis is divulged at the end of the vignette, after you have just struggled through the narrative to come up with a diagnosis of your own. The question might then ask about a related aspect of the diagnosed disease. Consider skimming the answer choices and lead-in before diving into a long stem. However, be careful with skimming the answer choices; going too fast may warp your perception of what the vignette is asking.

## IF YOU THINK YOU FAILED

After the test, many examinees feel that they have failed, and most are at the very least unsure of their pass/fail status. There are several sensible steps you can take to plan for the future in the event that you do not achieve a passing score. First, save and organize all your study materials, including review books, practice tests, and notes. Familiarize yourself with the reapplication procedures for Step 1, including application deadlines and upcoming test dates.

Make sure you know both your school's and the NBME's policies regarding retakes. The NBME allows a maximum of six attempts to pass each Step examination.[18] You may take Step 1 no more than three times within a 12-month period. Your fourth and subsequent attempts must be at least 12 months after your first attempt at that exam and at least six months after your most recent attempt at that exam. No earlier than July 1, 2021, the total number of attempts an examinee may take per Step examination will be reduced to four attempts.

*If you pass Step 1 (score of 194 or above), you are not allowed to retake the exam.*

The performance profiles on the back of the USMLE Step 1 score report provide valuable feedback concerning your relative strengths and weaknesses. Study these profiles closely. Set up a study timeline to strengthen gaps in your knowledge as well as to maintain and improve what you already know. Do not neglect high-yield subjects. It is normal to feel somewhat anxious about retaking the test, but if anxiety becomes a problem, seek appropriate counseling.

## ▶ TESTING AGENCIES

- **National Board of Medical Examiners (NBME) / USMLE Secretariat**
  Department of Licensing Examination Services
  3750 Market Street
  Philadelphia, PA 19104-3102
  (215) 590-9500 (operator) or
  (215) 590-9700 (automated information line)
  Email: webmail@nbme.org
  www.nbme.org

- **Educational Commission for Foreign Medical Graduates (ECFMG)**
  3624 Market Street
  Philadelphia, PA 19104-2685
  (215) 386-5900
  Email: info@ecfmg.org
  www.ecfmg.org

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# Special Situations

Please visit **www.firstaidteam.com/bonus/** to view this section.

## NOTES

SECTION II

# High-Yield General Principles

*"I've learned that I still have a lot to learn."*

—Maya Angelou

*"Never regard study as a duty, but as the enviable opportunity to learn."*

—Albert Einstein

*"Live as if you were to die tomorrow. Learn as if you were to live forever."*

—Gandhi

*"Success is the maximum utilization of the ability that you have."*

—Zig Ziglar

## ▶ HOW TO USE THE DATABASE

The 2021 edition of *First Aid for the USMLE Step 1* contains a revised and expanded database of basic science material that students, student authors, and faculty authors have identified as high yield for board review. The information is presented in a partially organ-based format. Hence, Section II is devoted to the foundational principles of biochemistry, microbiology, immunology, basic pathology, basic pharmacology, and public health sciences. Section III focuses on organ systems, with subsections covering the embryology, anatomy and histology, physiology, clinical pathology, and clinical pharmacology relevant to each. Each subsection is then divided into smaller topic areas containing related facts. Individual facts are generally presented in a three-column format, with the **Title** of the fact in the first column, the **Description** of the fact in the second column, and the **Mnemonic** or **Special Note** in the third column. Some facts do not have a mnemonic and are presented in a two-column format. Others are presented in list or tabular form in order to emphasize key associations.

The database structure used in Sections II and III is useful for reviewing material already learned. These sections are **not** ideal for learning complex or highly conceptual material for the first time.

The database of high-yield facts is not comprehensive. Use it to complement your core study material and not as your primary study source. The facts and notes have been condensed and edited to emphasize the high-yield material, and as a result, each entry is "incomplete" and arguably "over-simplified." Often, the more you research a topic, the more complex it becomes, with certain topics resisting simplification. Determine your most efficient methods for learning the material, and do not be afraid to abandon a strategy if it is not working for you.

Our database of high-yield facts is updated annually to keep current with new trends in boards emphasis, including clinical relevance. However, we must note that inevitably many other high-yield topics are not yet included in our database.

We actively encourage medical students and faculty to submit high-yield topics, well-written entries, diagrams, clinical images, and useful mnemonics so that we may enhance the database for future students. We also solicit recommendations of alternate tools for study that may be useful in preparing for the examination, such as charts, flash cards, apps, and online resources (see How to Contribute, p. xvii).

### Image Acknowledgments

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### Disclaimer

The entries in this section reflect student opinions on what is high yield. Because of the diverse sources of material, no attempt has been made to trace or reference the origins of entries individually. We have regarded mnemonics as essentially in the public domain. Errata will gladly be corrected if brought to the attention of the authors, either through our online errata submission form at www.firstaidteam.com or directly by email to firstaid@scholarrx.com.

NOTES

HIGH-YIELD PRINCIPLES IN

# Biochemistry

*"The nitrogen in our DNA, the calcium in our teeth, the iron in our blood, the carbon in our apple pies were made in the interiors of collapsing stars. We are made of starstuff."*

—Carl Sagan

*"Biochemistry is the study of carbon compounds that crawl."*

—Mike Adams

*"We think we have found the basic mechanism by which life comes from life."*

—Francis H. C. Crick

*DNA was the first three-dimensional Xerox machine.*

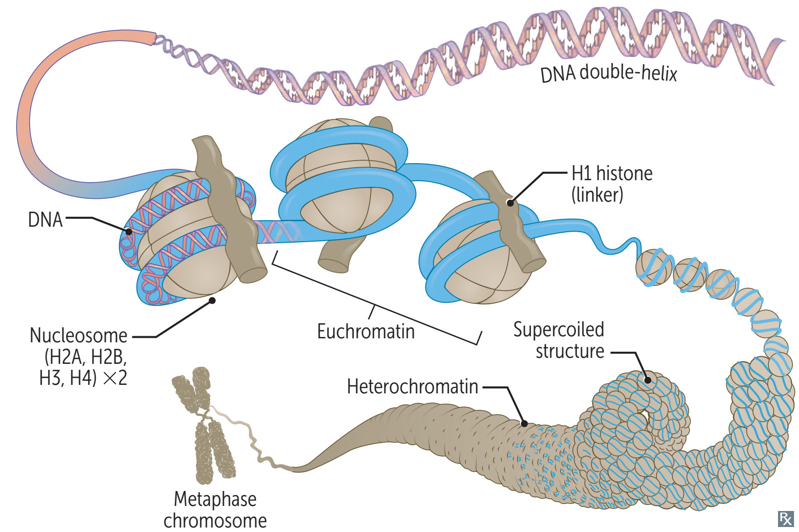
—Kenneth Ewart Boulding

This high-yield material includes molecular biology, genetics, cell biology, and principles of metabolism (especially vitamins, cofactors, minerals, and single-enzyme-deficiency diseases). When studying metabolic pathways, emphasize important regulatory steps and enzyme deficiencies that result in disease, as well as reactions targeted by pharmacologic interventions. For example, understanding the defect in Lesch-Nyhan syndrome and its clinical consequences is higher yield than memorizing every intermediate in the purine salvage pathway.

Do not spend time learning details of organic chemistry, mechanisms, or physical chemistry. Detailed chemical structures are infrequently tested; however, many structures have been included here to help students learn reactions and the important enzymes involved. Familiarity with the biochemical techniques that have medical relevance—such as ELISA, immunoelectrophoresis, Southern blotting, and PCR—is useful. Review the related biochemistry when studying pharmacology or genetic diseases as a way to reinforce and integrate the material.

## ▸ BIOCHEMISTRY—MOLECULAR

### Chromatin structure

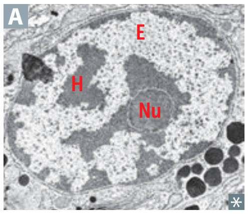



DNA exists in the condensed, chromatin form to fit into the nucleus. DNA loops twice around a histone octamer to form a nucleosome (“beads on a string”). H1 binds to the nucleosome and to “linker DNA,” thereby stabilizing the chromatin fiber.

Phosphate groups give DNA a ⊖ charge. Lysine and arginine give histones a ⊕ charge.

In mitosis, DNA condenses to form chromosomes. DNA and histone synthesis occurs during S phase.

Mitochondria have their own DNA, which is circular and does not utilize histones.

| | | |
|---|---|---|
| **Heterochromatin**   | Condensed, appears darker on EM (labeled H in A; Nu, nucleolus). Sterically inaccessible, thus transcriptionally inactive. ↑ methylation, ↓ acetylation. | **H**etero**c**hromatin = **h**ighly **c**ondensed.<br>Barr bodies (inactive X chromosomes) may be visible on the periphery of nucleus. |
| **Euchromatin** | Less condensed, appears lighter on EM (labeled E in A). Transcriptionally active, sterically accessible. | *Eu* = true, “truly transcribed.”<br>**E**uchromatin is **e**xpressed. |
| **DNA methylation** | Changes the expression of a DNA segment without changing the sequence. Involved with aging, carcinogenesis, genomic imprinting, transposable element repression, and X chromosome inactivation (lyonization). | DNA is methylated in imprinting.<br>Methylation within gene promoter (CpG islands) typically represses (silences) gene transcription.<br>CpG **m**ethylation **m**akes DNA **m**ute. |
| **Histone methylation** | Usually causes reversible transcriptional suppression, but can also cause activation depending on location of methyl groups. | Histone **m**ethylation **m**ostly **m**akes DNA **m**ute. |
| **Histone acetylation** | Removal of histone’s ⊕ charge → relaxed DNA coiling → ↑ transcription. | Thyroid hormone receptors alter thyroid hormone synthesis by acetylation. Dysregulated acetylation is implicated in Huntington disease.<br>Histone **a**cetylation makes DNA **a**ctive. |
| **Histone deacetylation** | Removal of acetyl groups → tightened DNA coiling → ↓ transcription. | |

## Nucleotides

Nucleoside = base + (deoxy)ribose (**s**ugar).
Nucleo**t**ide = base + (deoxy)ribose + phospha**t**e; linked by 3′-5′ phosphodiester bond.

5′ end of incoming nucleotide bears the triphosphate (energy source for the bond). α-Phosphate is target of 3′ hydroxyl attack.

**Pur**ines (**A**,**G**)—2 rings.
**Pyr**imidines (**C**,**U**,**T**)—1 ring.

**Pur**e **A**s **G**old.
**CUT** the **pyr**amid.
**Thy**mine has a me**thy**l.

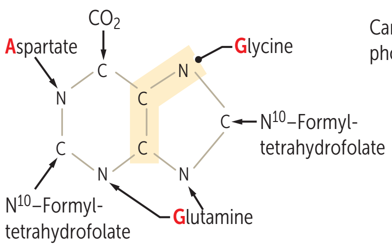
Deamination reactions:
- Cytosine → uracil
- Adenine → hypoxanthine
- Guanine → xanthine
- 5-methylcytosine → thymine

C-G bond (3 H bonds) stronger than A-T bond (2 H bonds). ↑ C-G content → ↑ melting temperature of DNA. "**C**-**G** bonds are like **C**razy **G**lue."

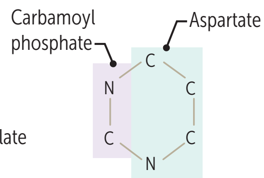
Uracil found in RNA; thymine in DNA. Methylation of uracil makes thymine.

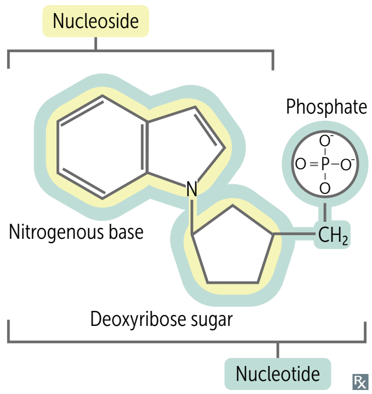
Amino acids necessary for **pur**ine synthesis (cats **purr** until they **GAG**):
- **G**lycine
- **A**spartate
- **G**lutamine

Purine (A, G)



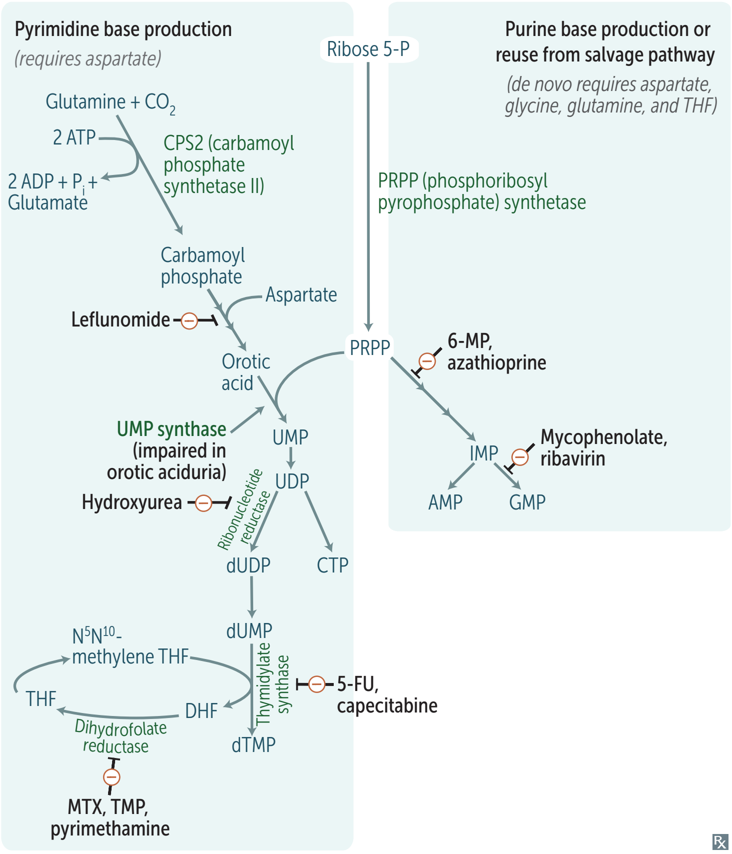

Pyrimidine (C, U, T)



## De novo pyrimidine and purine synthesis

Various immunosuppressive, antineoplastic, and antibiotic drugs function by interfering with nucleotide synthesis:



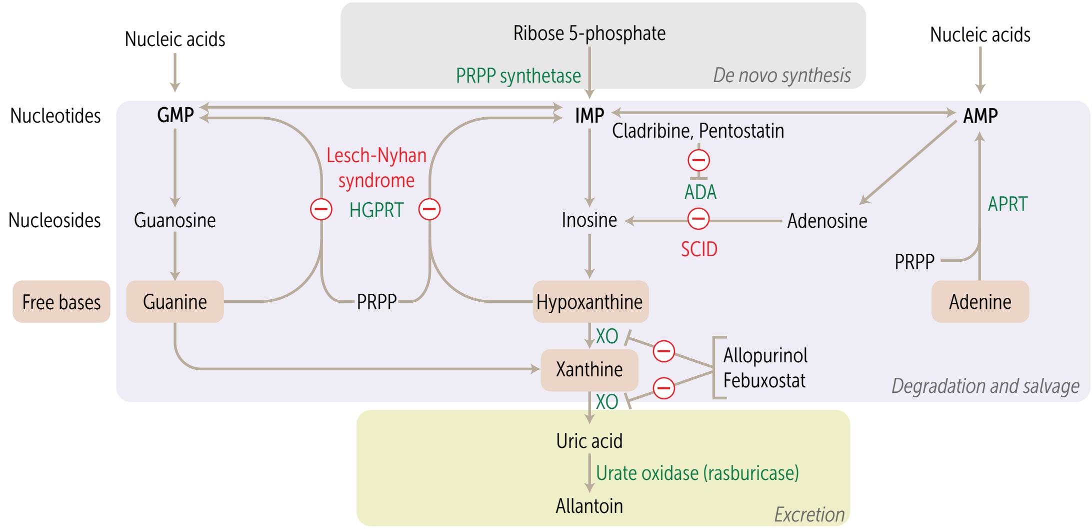

**Pyrimidine synthesis:**
- Leflunomide: inhibits dihydroorotate dehydrogenase
- 5-fluorouracil (5-FU) and its prodrug capecitabine: form 5-F-dUMP, which inhibits thymidylate synthase (↓ dTMP)

**Purine synthesis:**
- 6-mercaptopurine (6-MP) and its prodrug azathioprine: inhibit de novo purine synthesis
- Mycophenolate and ribavirin: inhibit inosine monophosphate dehydrogenase

**Purine and pyrimidine synthesis:**
- Hydroxyurea: inhibits ribonucleotide reductase
- Methotrexate (MTX), trimethoprim (TMP), and pyrimethamine: inhibit dihydrofolate reductase (↓ deoxythymidine monophosphate [dTMP]) in humans, bacteria, and protozoa, respectively

CPS1 = m1tochondria (urea cycle)
CPS2 = cytwosol

## Purine salvage deficiencies




ADA, adenosine deaminase; APRT, adenine phosphoribosyltransferase; HGPRT, hypoxanthine guanine phosphoribosyltransferase, XO, xanthine oxidase; SCID, severe combined immune deficiency (autosomal recessive inheritance)

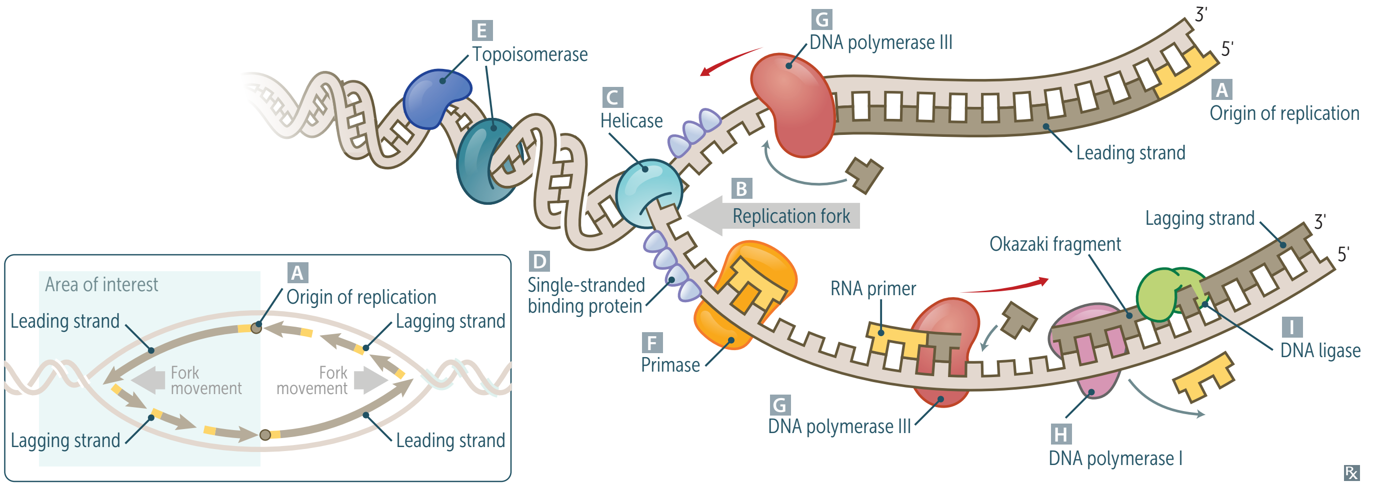
| | | |
|---|---|---|
| **Adenosine deaminase deficiency** | ADA is required for degradation of adenosine and deoxyadenosine. ↓ ADA → ↑ dATP → ↓ ribonucleotide reductase activity → ↓ DNA precursors in cells → ↓ lymphocytes. | One of the major causes of autosomal recessive SCID. |
| **Lesch-Nyhan syndrome** | Defective purine salvage due to absent **HGPRT**, which converts hypoxanthine to IMP and guanine to GMP. ↑ purine synthesis (↑ PRPP aminotransferase activity) → excess uric acid production. X-linked recessive.<br>Findings: intellectual disability, self-mutilation, aggression, hyperuricemia (red/orange "sand" [sodium urate crystals] in diaper), gout, dystonia, macrocytosis. | **HGPRT**:<br>**H**yperuricemia<br>**G**out<br>**P**issed off (aggression, self-mutilation)<br>**R**ed/orange crystals in urine<br>**T**ense muscles (dystonia)<br>Treatment: allopurinol or febuxostat (2nd line). |

## Genetic code features

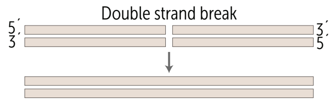
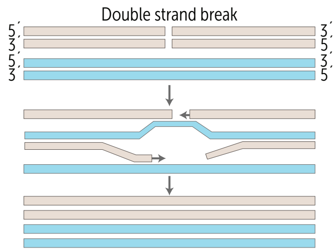
| | | |
|---|---|---|
| **Unambiguous** | Each codon specifies only 1 amino acid. | |
| **Degenerate/ redundant** | Most amino acids are coded by multiple codons.<br>**Wobble**—codons that differ in 3rd ("wobble") position may code for the same tRNA/amino acid. Specific base pairing is usually required only in the first 2 nucleotide positions of mRNA codon. | Exceptions: methionine (AUG) and tryptophan (UGG) encoded by only 1 codon. |
| **Commaless, nonoverlapping** | Read from a fixed starting point as a continuous sequence of bases. | Exceptions: some viruses. |
| **Universal** | Genetic code is conserved throughout evolution. | Exception in humans: mitochondria. |

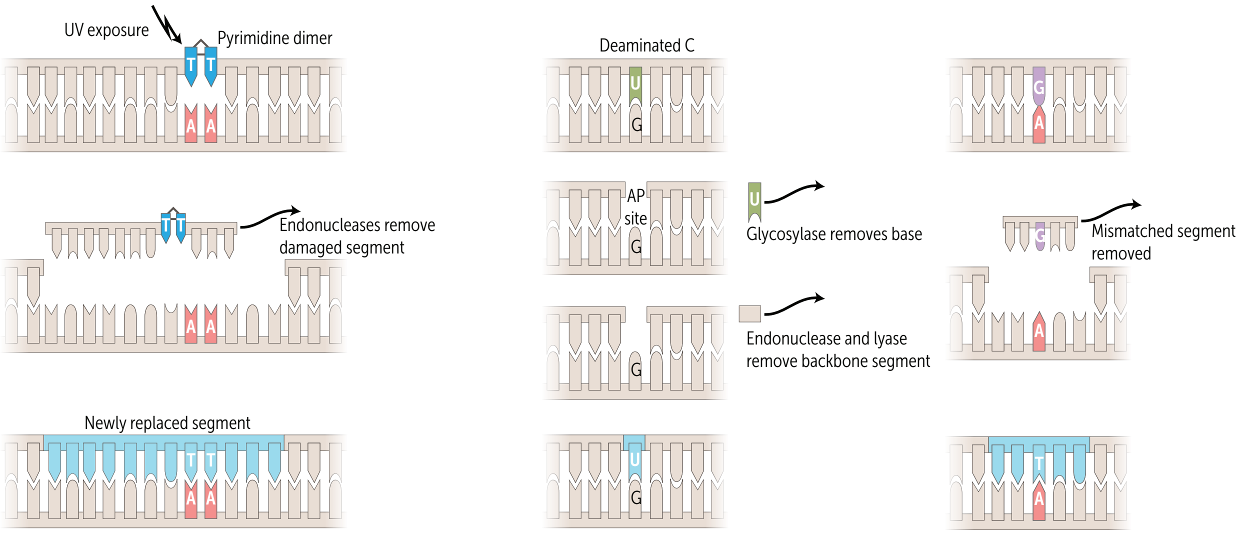
**DNA replication** Occurs in 5′ → 3′ direction ("5ynth3sis") in continuous and discontinuous (Okazaki fragment) fashion. Semiconservative. More complex in eukaryotes than in prokaryotes, but shares analogous enzymes.

| | | |
|---|---|---|
| **Origin of replication** A | Particular consensus sequence in genome where DNA replication begins. May be single (prokaryotes) or multiple (eukaryotes). | AT-rich sequences (such as TATA box regions) are found in promoters and origins of replication. |
| **Replication fork** B | Y-shaped region along DNA template where leading and lagging strands are synthesized. | |
| **Helicase** C | Unwinds DNA template at replication fork. | **H**elicase **h**alves DNA.<br>Deficient in **Bloom** syndrome (***BLM*** gene mutation). |
| **Single-stranded binding proteins** D | Prevent strands from reannealing or degradation by nucleases. | |
| **DNA topoisomerases** E | Creates a **single**- (topoisomerase **I**) or **double**- (topoisomerase **II**) stranded break in the helix to add or remove supercoils (as needed due to underwinding or overwinding of DNA). | In eukaryotes: irinotecan/topotecan inhibit topoisomerase (TOP) I, etoposide/teniposide inhibit TOP II.<br>In prokaryotes: fluoroquinolones inhibit TOP II (DNA gyrase) and TOP IV. |
| **Primase** F | Makes an RNA primer on which DNA polymerase III can initiate replication. | |
| **DNA polymerase III** G | Prokaryotes only. Elongates leading strand by adding deoxynucleotides to the 3′ end. Elongates lagging strand until it reaches primer of preceding fragment. | DNA polymerase III has 5′ → 3′ synthesis and proofreads with 3′ → 5′ exonuclease.<br>Drugs blocking DNA replication often have a modified 3′ OH, thereby preventing addition of the next nucleotide ("chain termination"). |
| **DNA polymerase I** H | Prokaryotes only. Degrades RNA primer; replaces it with DNA. | Same functions as DNA polymerase III, also excises RNA primer with 5′ → 3′ exonuclease. |
| **DNA ligase** I | Catalyzes the formation of a phosphodiester bond within a strand of double-stranded DNA. | Joins Okazaki fragments.<br>**L**igase **l**inks DNA. |
| **Telomerase** | Eukaryotes only. A reverse transcriptase (RNA-dependent DNA polymerase) that adds DNA (**TTAGGG**) to 3′ ends of chromosomes to avoid loss of genetic material with every duplication. | Often upregulated in cancer, downregulated in aging and progeria.<br>**T**elomerase **TAG**s for **G**reatness and **G**lory. |



### DNA repair

| | | |
|---|---|---|
| **Double strand** | | |
| **Nonhomologous end joining** | Brings together 2 ends of DNA fragments to repair double-stranded breaks.<br>Defective in ataxia-telangiectasia.<br>Homology not required. Some DNA may be lost. | <br>Nonhomologous end joining |
| **Homologous recombination** | Requires 2 homologous DNA duplexes. A strand from damaged dsDNA is repaired using a complementary strand from intact homologous dsDNA as a template.<br>Defective in breast/ovarian cancers with *BRCA1* mutation and in Fanconi anemia.<br>Restores duplexes accurately without loss of nucleotides. | <br>Homologous recombination |
| **Single strand** | | |
| **Nucleotide excision repair** | Specific endonucleases release the oligonucleotides containing damaged bases; DNA polymerase and ligase fill and reseal the gap, respectively. Repairs bulky helix-distorting lesions. | Occurs in $G_1$ phase of cell cycle.<br>Defective in xeroderma pigmentosum (inability to repair DNA pyrimidine dimers caused by UV exposure). Presents with dry skin, photosensitivity, skin cancer. |
| **Base excision repair** | Base-specific **G**lycosylase removes altered base and creates AP site (apurinic/apyrimidinic). One or more nucleotides are removed by AP-**E**ndonuclease, which cleaves 5′ end. AP-**L**yase cleaves 3′ end. DNA **P**olymerase-β fills the gap and DNA **l**igase seals it. | Occurs throughout cell cycle.<br>Important in repair of spontaneous/toxic deamination.<br>"**GEL Pl**ease." |
| **Mismatch repair** | Mismatched nucleotides in newly synthesized (unmethylated) strand are removed and gap is filled and resealed. | Occurs predominantly in S phase of cell cycle.<br>Defective in Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]). |




Nucleotide excision repair    Base excision repair    Mismatch repair

**Mutations in DNA** — Degree of change: silent << missense < nonsense < frameshift. Single nucleotide substitutions are repaired by DNA polymerase and DNA ligase. Types of single nucleotide (point) mutations:
- Transition—purine to purine (eg, A to G) or pyrimidine to pyrimidine (eg, C to T).
- Transversion—purine to pyrimidine (eg, A to T) or pyrimidine to purine (eg, C to G).

### Single nucleotide substitutions

**Silent mutation** — Codes for same (synonymous) amino acid; often involves 3rd position of codon (tRNA wobble).

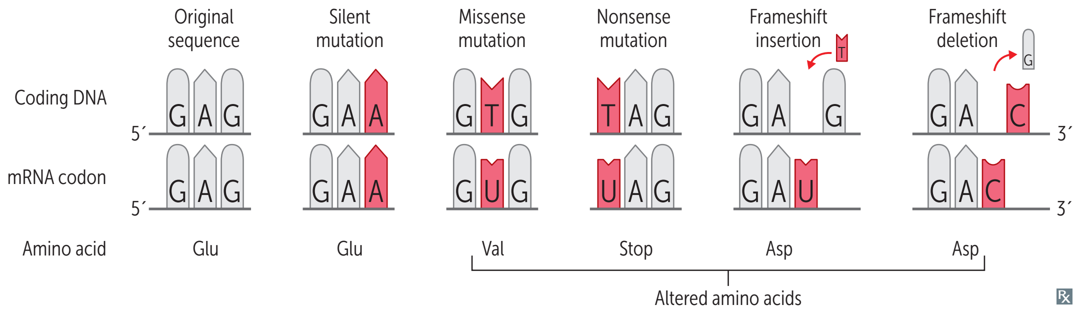
**Missense mutation** — Results in changed amino acid (called conservative if new amino acid has similar chemical structure). Examples: sickle cell disease (substitution of glutamic acid with valine).

**Nonsense mutation** — Results in early **stop** codon (UGA, UAA, UAG). Usually generates nonfunctional protein. **Stop** the **nonsense**!

### Other mutations

**Frameshift mutation** — Deletion or insertion of any number of nucleotides not divisible by 3 → misreading of all nucleotides downstream. Protein may be shorter or longer, and its function may be disrupted or altered. Examples: Duchenne muscular dystrophy, Tay-Sachs disease.

**Splice site mutation** — Retained intron in mRNA → protein with impaired or altered function. Examples: rare causes of cancers, dementia, epilepsy, some types of β-thalassemia, Gaucher disease, Marfan syndrome.

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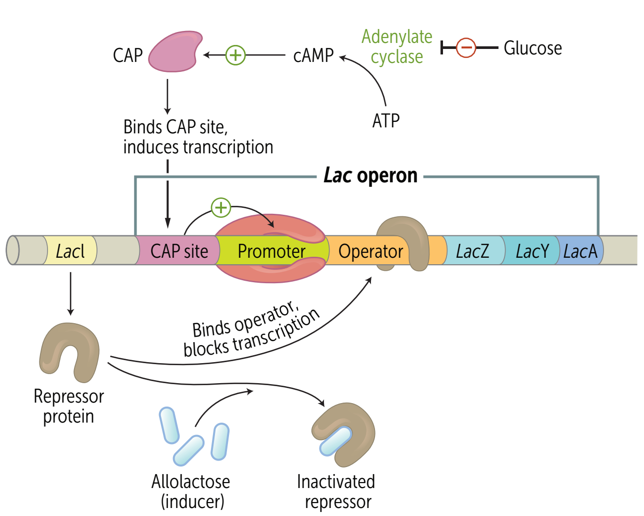
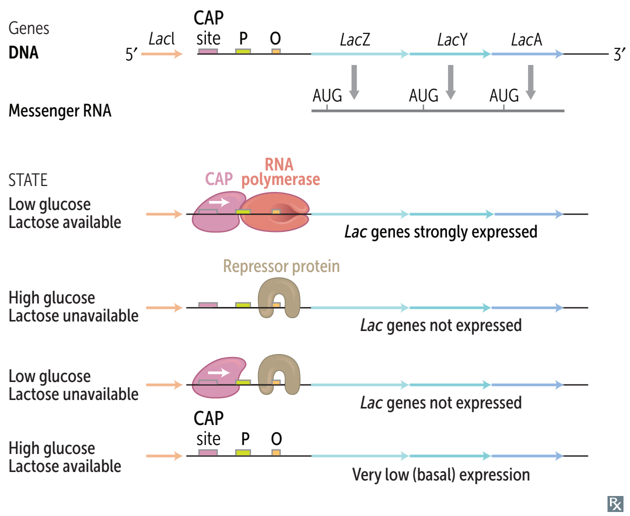
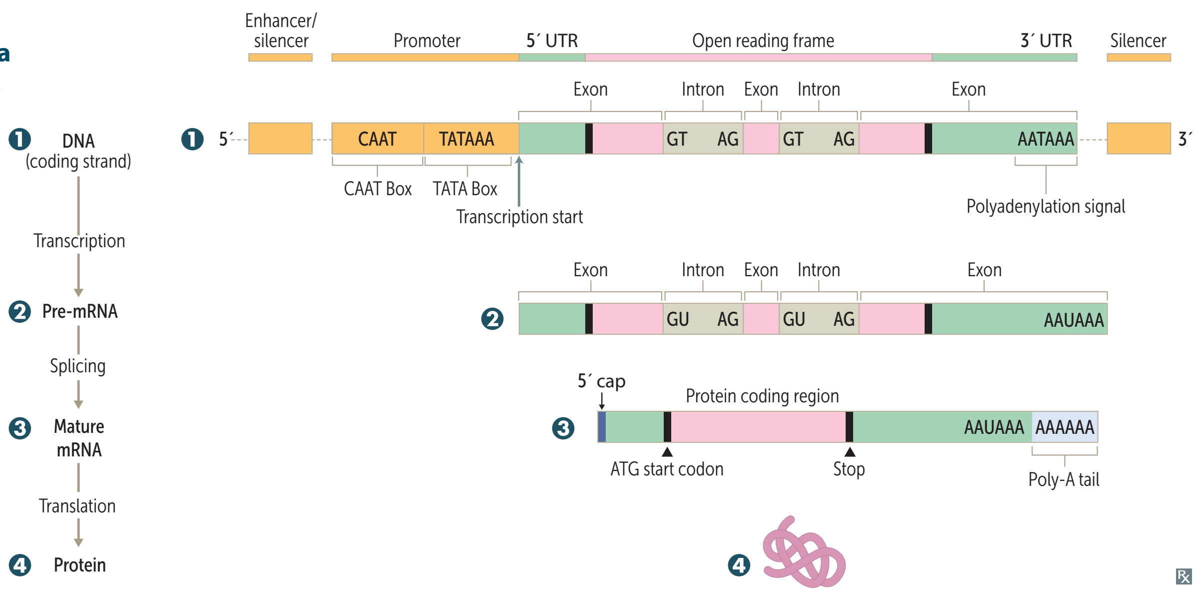
## *Lac* operon

Classic example of a genetic response to an environmental change. Glucose is the preferred metabolic substrate in *E coli*, but when glucose is absent and lactose is available, the *lac* operon is activated to switch to lactose metabolism. Mechanism of shift:
- Low glucose → ↑ adenylate cyclase activity → ↑ generation of cAMP from ATP → activation of catabolite activator protein (CAP) → ↑ transcription.
- High lactose → unbinds repressor protein from repressor/operator site → ↑ transcription.



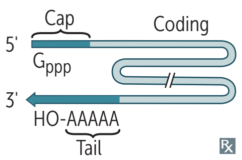



## Functional organization of a eukaryotic gene




## Regulation of gene expression

| | | |
|---|---|---|
| **Promoter** | Site where RNA polymerase II and multiple other transcription factors bind to DNA upstream from gene locus (AT-rich upstream sequence with TATA and CAAT boxes, which differ between eukaryotes and prokaryotes). | Promoter mutation commonly results in dramatic ↓ in level of gene transcription. |
| **Enhancer** | DNA locus where regulatory proteins ("**activators**") bind, **increasing** expression of a gene on the same chromosome. | Enhancers and silencers may be located close to, far from, or even within (in an intron) the gene whose expression they regulate. |
| **Silencer** | DNA locus where regulatory proteins ("**repressors**") bind, **decreasing** expression of a gene on the same chromosome. | |

| | | |
|---|---|---|
| **RNA processing (eukaryotes)**   | Initial transcript is called heterogeneous nuclear RNA (hnRNA). hnRNA is then modified and becomes mRNA.<br>The following processes occur in the nucleus:<br>▪ Capping of 5′ end (addition of 7-methylguanosine cap)<br>▪ Polyadenylation of 3′ end (~ 200 A's → poly-A tail)<br>▪ Splicing out of introns<br>Capped, tailed, and spliced transcript is called mRNA. | mRNA is transported out of nucleus to be translated in cytosol.<br>mRNA quality control occurs at cytoplasmic processing bodies (P-bodies), which contain exonucleases, decapping enzymes, and microRNAs; mRNAs may be degraded or stored in P-bodies for future translation.<br>Poly-A polymerase does not require a template.<br>AAUAAA = polyadenylation signal. |

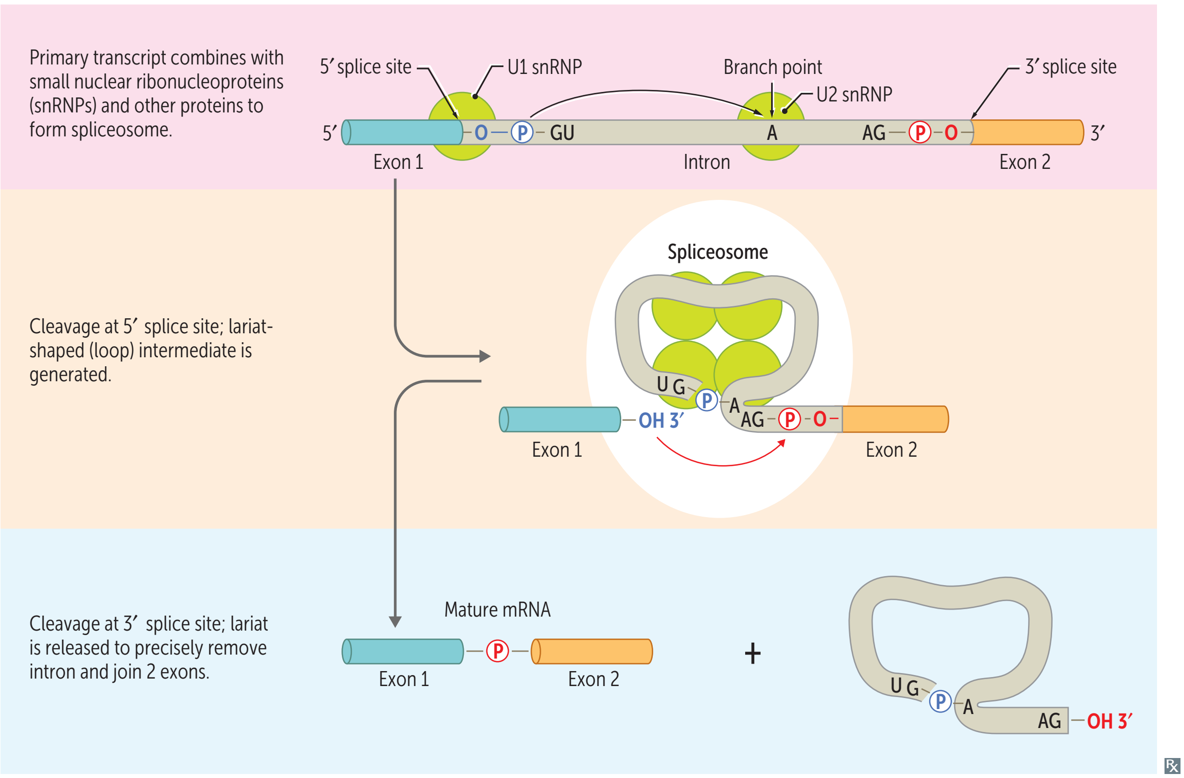
## RNA polymerases

| | | |
|---|---|---|
| Eukaryotes | RNA polymerase I makes **r**RNA, the most common (**r**ampant) type; present only in nucleolus.<br>RNA polymerase II makes **m**RNA (**m**assive), **mic**roRNA (**mi**RNA), and **s**mall **n**uclear RNA (**sn**RNA).<br>RNA polymerase III makes 5S rRNA, **t**RNA (**t**iny).<br>No proofreading function, but can initiate chains. RNA polymerase II opens DNA at promoter site. | I, II, and III are numbered in the same order that their products are used in protein synthesis: rRNA, mRNA, then tRNA.<br>α-amanitin, found in *Amanita phalloides* (death cap mushrooms), inhibits RNA polymerase II. Causes dysentery and severe hepatotoxicity if ingested.<br>Actinomycin D, also called dactinomycin, inhibits RNA polymerase in both prokaryotes and eukaryotes. |
| Prokaryotes | 1 RNA polymerase (multisubunit complex) makes all 3 kinds of RNA. | Rifamycins (rifampin, rifabutin) inhibit DNA-dependent RNA polymerase in prokaryotes. |

## Splicing of pre-mRNA

Part of process by which precursor mRNA (pre-mRNA) is transformed into mature mRNA. Alterations in snRNP assembly can cause clinical disease; eg, in spinal muscular atrophy, snRNP assembly is affected due to ↓ SMN protein → congenital degeneration of anterior horns of spinal cord → symmetric weakness (hypotonia, or “floppy baby syndrome”).

Anti-U1 snRNP antibodies are associated with SLE, mixed connective tissue disease, other rheumatic diseases.



## Introns vs exons

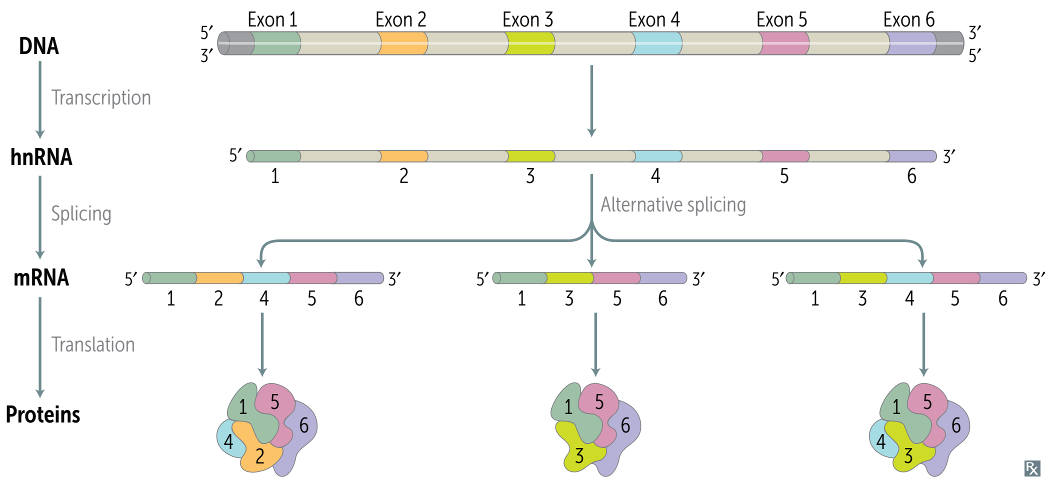
Exons contain the actual genetic information coding for protein.

Introns do not code for protein, but are important in regulation of gene expression.

Different exons are frequently combined by alternative splicing to produce a larger number of unique proteins.

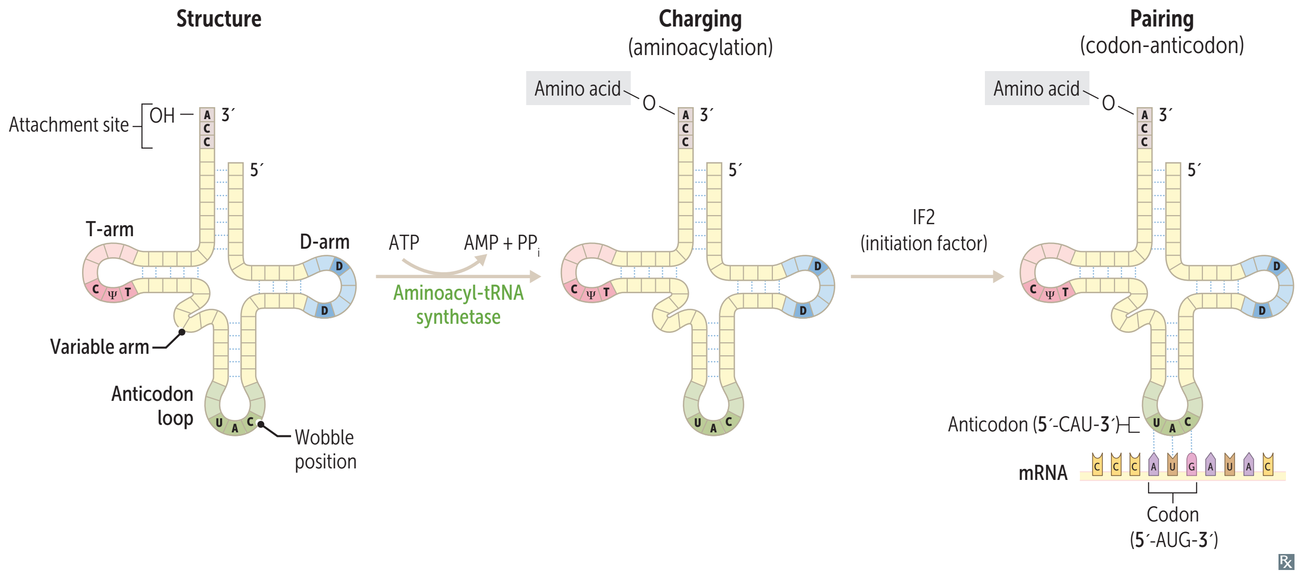
Alternative splicing can produce a variety of protein products from a single hnRNA (heterogenous nuclear RNA) sequence (eg, transmembrane vs secreted Ig, tropomyosin variants in muscle, dopamine receptors in the brain, host defense evasion by tumor cells).

**In**trons are **in**tervening sequences and stay **in** the nucleus, whereas **ex**ons **ex**it and are **ex**pressed.



## tRNA

| | |
|---|---|
| **Structure** | 75–90 nucleotides, 2° structure, cloverleaf form, anticodon end is opposite 3′ aminoacyl end. All tRNAs, both eukaryotic and prokaryotic, have CCA at 3′ end along with a high percentage of chemically modified bases. The amino acid is covalently bound to the 3′ end of the tRNA. **CCA Can Carry Amino** acids.<br>T-arm: contains the TΨC (ribothymidine, pseudouridine, cytidine) sequence necessary for tRNA-ribosome binding. **T**-arm **T**ethers tRNA molecule to ribosome.<br>D-arm: contains **D**ihydrouridine residues necessary for tRNA recognition by the correct aminoacyl-tRNA synthetase. **D**-arm allows **D**etection of the tRNA by aminoacyl-tRNA synthetase.<br>Attachment site: 3′-**ACC**-5′ is the amino acid **ACC**eptor site. |
| **Charging** | Aminoacyl-tRNA synthetase (uses ATP; 1 unique enzyme per respective amino acid) and binding of charged tRNA to the codon are responsible for the accuracy of amino acid selection. Aminoacyl-tRNA synthetase matches an amino acid to the tRNA by scrutinizing the amino acid before and after it binds to tRNA. If an incorrect amino acid is attached, the bond is hydrolyzed.<br>A mischarged tRNA reads the usual codon but inserts the wrong amino acid. |

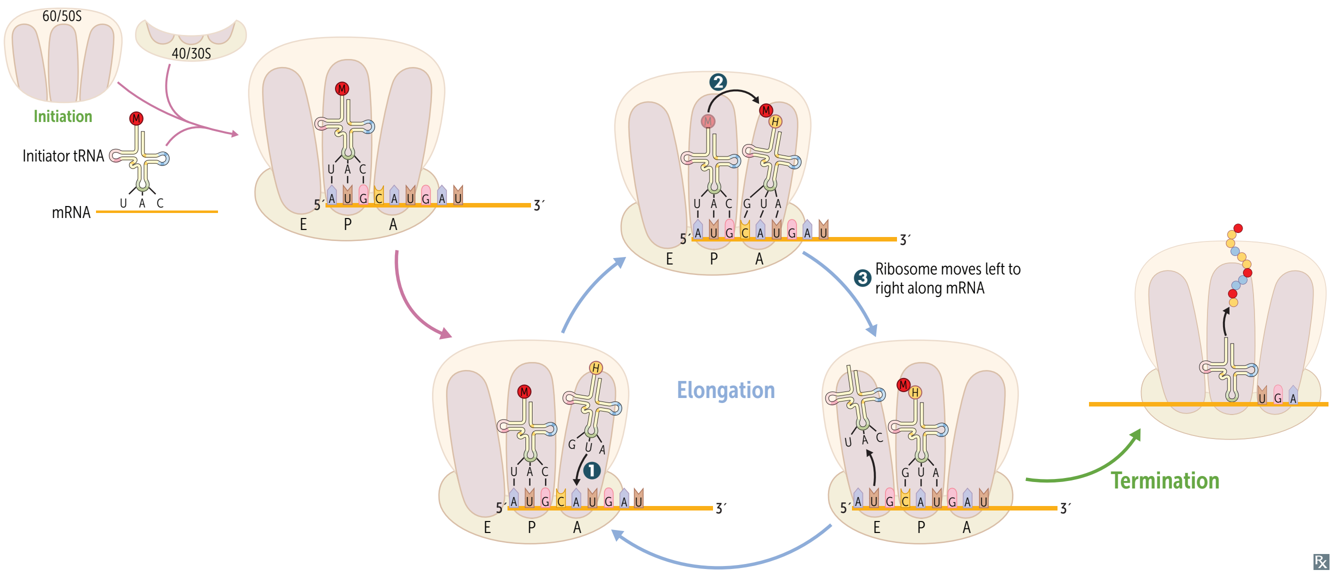



## Start and stop codons

| | | |
|---|---|---|
| **mRNA start codons** | AUG. | **AUG** in**AUG**urates protein synthesis. |
| Eukaryotes | Codes for methionine, which may be removed before translation is completed. | |
| Prokaryotes | Codes for N-formylmethionine (fMet). | fMet stimulates neutrophil chemotaxis. |
| **mRNA stop codons** | UGA, UAA, UAG. | **UGA** = **U G**o **A**way.<br>**UAA** = **U A**re **A**way.<br>**UAG** = **U A**re **G**one. |

## Protein synthesis

| | | |
|---|---|---|
| **Initiation** | 1. Eukaryotic initiation factors (eIFs) identify the 5′ cap.<br>2. eIFs help assemble the 40S ribosomal subunit with the initiator tRNA.<br>3. eIFs released when the mRNA and the ribosomal 60S subunit assemble with the complex. Requires GTP. | Eukaryotes: 40S + 60S → 80S (even).<br>Prokaryotes: 30S + 50S → 70S (prime).<br>Synthesis occurs from N-terminus to C-terminus.<br><br>ATP—tRNA Activation (charging).<br>GTP—tRNA Gripping and Going places (translocation). |
| **Elongation** | ❶ Aminoacyl-tRNA binds to A site (except for initiator methionine, which binds the P site), requires an elongation factor and GTP.<br>❷ rRNA ("ribozyme") catalyzes peptide bond formation, transfers growing polypeptide to amino acid in A site.<br>❸ Ribosome advances 3 nucleotides toward 3′ end of mRNA, moving peptidyl tRNA to P site (translocation). | Think of "going APE":<br>A site = incoming Aminoacyl-tRNA.<br>P site = accommodates growing Peptide.<br>E site = holds Empty tRNA as it Exits.<br><br>Elongation factors are targets of bacterial toxins (eg, *Diphtheria*, *Pseudomonas*). |
| **Termination** | Eukaryotic release factors (eRFs) recognize the stop codon and halt translation → completed polypeptide is released from ribosome. Requires GTP. | Shine-Dalgarno sequence—ribosomal binding site in prokaryotic mRNA. Enables protein synthesis initiation by aligning the ribosome with the start codon so that code is read correctly. |




## Posttranslational modifications

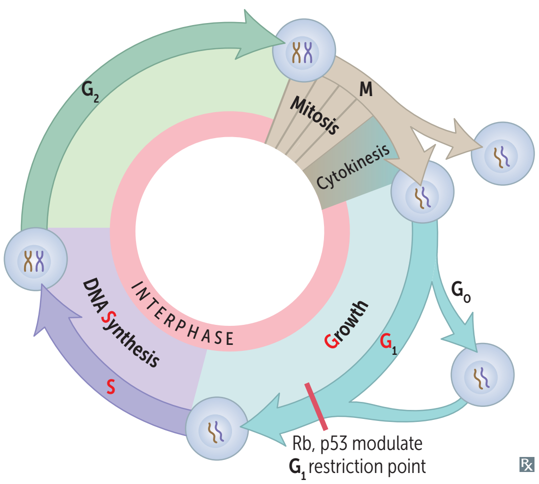
| | |
|---|---|
| **Trimming** | Removal of N- or C-terminal propeptides from zymogen to generate mature protein (eg, trypsinogen to trypsin). |
| **Covalent alterations** | Phosphorylation, glycosylation, hydroxylation, methylation, acetylation, and ubiquitination. |

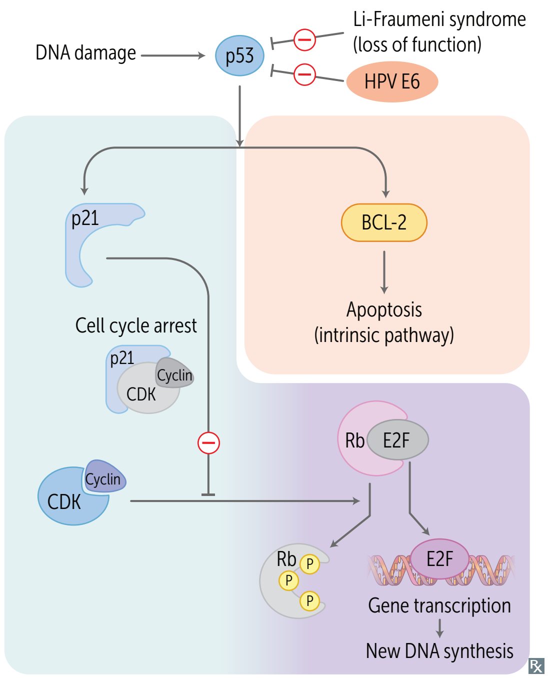
| | |
|---|---|
| **Chaperone protein** | Intracellular protein involved in facilitating and maintaining protein folding. In yeast, heat shock proteins (eg, HSP60) are constitutively expressed, but expression may increase with high temperatures, acidic pH, and hypoxia to prevent protein denaturing/misfolding. |

## ▶ BIOCHEMISTRY—CELLULAR

| | |
|---|---|
| **Cell cycle phases** | Checkpoints control transitions between phases of cell cycle. This process is regulated by cyclins, cyclin-dependent kinases (CDKs), and tumor suppressors. M phase (shortest phase of cell cycle) includes mitosis (prophase, prometaphase, metaphase, anaphase, telophase) and cytokinesis (cytoplasm splits in two). $G_1$ and $G_0$ are of variable duration. |
| REGULATION OF CELL CYCLE | |
| **Cyclin-dependent kinases** | Constitutively expressed but inactive when not bound to cyclin. |
| **Cyclin-CDK complexes** | Cyclins are phase-specific regulatory proteins that activate CDKs when stimulated by growth factors. The cyclin-CDK complex can then phosphorylate other proteins (eg, Rb) to coordinate cell cycle progression. This complex must be activated/inactivated at appropriate times for cell cycle to progress. |
| **Tumor suppressors** | p53 → p21 induction → CDK inhibition → Rb hypophosphorylation (activation) → $G_1$-S progression inhibition. Mutations in tumor suppressor genes can result in unrestrained cell division (eg, Li-Fraumeni syndrome).<br>Growth factors (eg, insulin, PDGF, EPO, EGF) bind tyrosine kinase receptors to transition the cell from $G_1$ to S phase. |

| CELL TYPES | | |
|---|---|---|
| **Permanent** | Remain in $G_0$, regenerate from stem cells. | Neurons, skeletal and cardiac muscle, RBCs. |
| **Stable (quiescent)** | Enter $G_1$ from $G_0$ when stimulated. | Hepatocytes, lymphocytes, PCT, periosteal cells. |
| **Labile** | Never go to $G_0$, divide rapidly with a short $G_1$. Most affected by chemotherapy. | Bone marrow, gut epithelium, skin, hair follicles, germ cells. |



**Rough endoplasmic reticulum**

Site of synthesis of secretory (exported) proteins and of N-linked oligosaccharide addition to lysosomal and other proteins.
Nissl bodies (RER in neurons)—synthesize peptide neurotransmitters for secretion.
Free ribosomes—unattached to any membrane; site of synthesis of cytosolic, peroxisomal, and mitochondrial proteins.

N-linked glycosylation occurs in the eNdoplasmic reticulum.
Mucus-secreting goblet cells of small intestine and antibody-secreting plasma cells are rich in RER.
Proteins within organelles (eg, ER, Golgi bodies, lysosomes) are formed in RER.

---

**Smooth endoplasmic reticulum**

Site of steroid synthesis and detoxification of drugs and poisons. Lacks surface ribosomes. Location of glucose-6-phosphatase (last step in both glycogenolysis and gluconeogenesis).

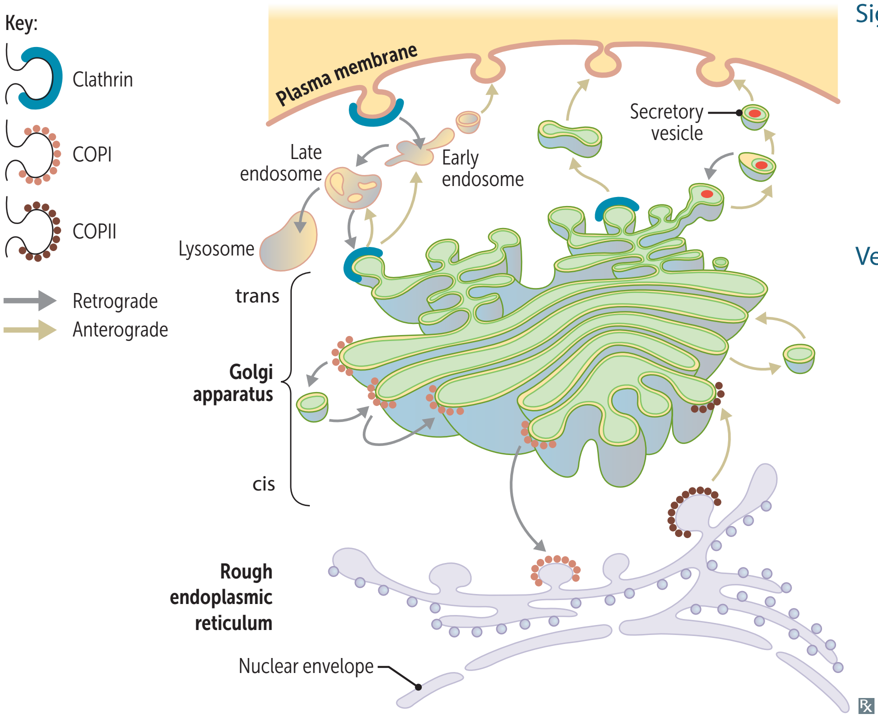
Liver hepatocytes and steroid hormone–producing cells of the adrenal cortex and gonads are rich in SER.

---

**Cell trafficking**

GOlgi is distribution center for proteins and lipids from ER to vesicles and plasma membrane. Posttranslational events in O-oligosaccharides include modifying N-oligosaccharides on asparagine, adding O-oligosaccharides on serine and threonine, and adding mannose-6-phosphate to proteins for lysosomal and other proteins.
Endosomes are sorting centers for material from outside the cell or from the Golgi, sending it to lysosomes for destruction or back to the membrane/Golgi for further use.

**I-cell disease** (inclusion cell disease/mucolipidosis type II)—inherited lysosomal storage disorder (autosomal recessive); defect in N-acetylglucosaminyl-1-phosphotransferase → failure of the Golgi to phosphorylate mannose residues (↓ mannose-6-phosphate) on glycoproteins → enzymes secreted extracellularly rather than delivered to lysosomes → lysosomes deficient in digestive enzymes → build-up of cellular debris in lysosomes (inclusion bodies). Results in coarse facial features, gingival hyperplasia, corneal clouding, restricted joint movements, claw hand deformities, kyphoscoliosis, and ↑ plasma levels of lysosomal enzymes. Often fatal in childhood.




**Signal recognition particle (SRP)**
Abundant, cytosolic ribonucleoprotein that traffics polypeptide-ribosome complex from the cytosol to the RER. Absent or dysfunctional SRP → accumulation of protein in cytosol.

**Vesicular trafficking proteins**
COPI: Golgi → Golgi (retrograde); *cis*-Golgi → ER.
COPII: ER → *cis*-Golgi (anterograde).
"Two (COPII) steps forward (anterograde); one (COPI) step back (retrograde)."
Clathrin: *trans*-Golgi → lysosomes; plasma membrane → endosomes (receptor-mediated endocytosis [eg, LDL receptor activity]).

**Peroxisome**

Membrane-enclosed organelle involved in:
- β-oxidation of very-long-chain fatty acids (VLCFA) (strictly peroxisomal process)
- α-oxidation of branched-chain fatty acids (strictly peroxisomal process)
- Catabolism of amino acids and ethanol
- Synthesis of cholesterol, bile acids, and plasmalogens (important membrane phospholipid, especially in white matter of brain)

Zellweger syndrome—autosomal recessive disorder of peroxisome biogenesis due to mutated *PEX* genes. Hypotonia, seizures, hepatomegaly, early death.

Refsum disease—autosomal recessive disorder of α-oxidation → buildup of phytanic acid due to inability to degrade it. Scaly skin, ataxia, cataracts/night blindness, shortening of 4th toe, epiphyseal dysplasia. Treatment: diet, plasmapheresis.

Adrenoleukodystrophy—X-linked recessive disorder of β-oxidation due to mutation in *ABCD1* gene → VLCFA buildup in **adrenal** glands, white (**leuko**) matter of brain, testes. Progressive disease that can lead to adrenal gland crisis, progressive loss of neurologic function, death.

**Proteasome**

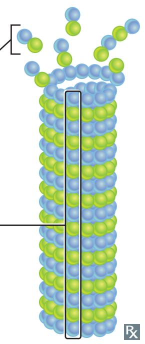
Barrel-shaped protein complex that degrades damaged or ubiquitin-tagged proteins. Defects in the ubiquitin-proteasome system have been implicated in some cases of Parkinson disease.

**Cytoskeletal elements**

A network of protein fibers within the cytoplasm that supports cell structure, cell and organelle movement, and cell division.

| TYPE OF FILAMENT | PREDOMINANT FUNCTION | EXAMPLES |
|---|---|---|
| **Microfilaments** | Muscle contraction, cytokinesis | Actin, microvilli. |
| **Intermediate filaments** | Maintain cell structure | Vimentin, desmin, cytokeratin, lamins, glial fibrillary acidic protein (GFAP), neurofilaments. |
| **Microtubules** | Movement, cell division | Cilia, flagella, mitotic spindle, axonal trafficking, centrioles. |

**Microtubule**




Cylindrical outer structure composed of a helical array of polymerized heterodimers of α- and β-tubulin. Each dimer has 2 GTP bound. Incorporated into flagella, cilia, mitotic spindles. Also involved in slow axoplasmic transport in neurons.

Molecular motor proteins—transport cellular cargo toward opposite ends of microtubule.
- **Ret**rograde to microtubule (+ → –)—**dy**nein.
- **A**nterograde to microtubule (– → +)—**k**inesin.

*Clostridium tetani* toxin, herpes simplex virus, poliovirus, and rabies virus use dynein for retrograde transport to the neuronal cell body.

Drugs that act on microtubules (**m**icrotubules **g**et **c**onstructed **v**ery **t**erribly):
- **M**ebendazole (antihelminthic)
- **G**riseofulvin (antifungal)
- **C**olchicine (antigout)
- **V**inca alkaloids (anticancer)
- **T**axanes (anticancer)

**N**egative end **n**ear **n**ucleus.
**P**ositive end **p**oints to **p**eriphery.

**Ready**? **A**ttac**k**!

**Cilia structure**

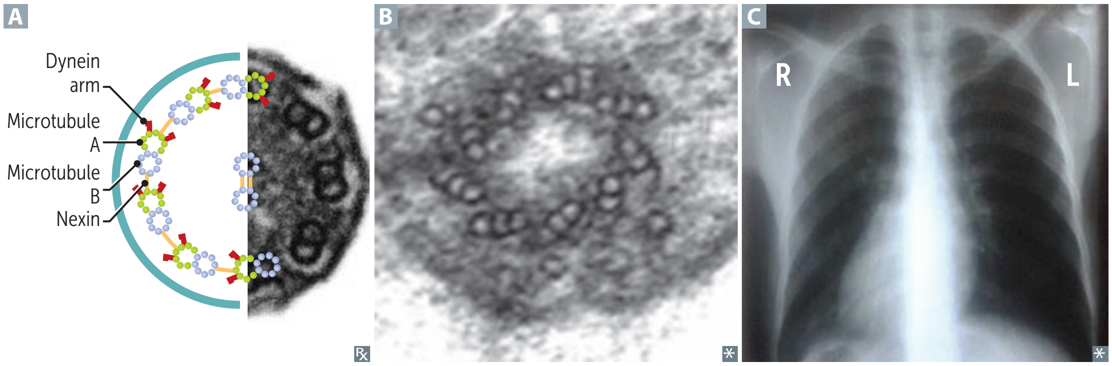
9 doublet + 2 singlet arrangement of microtubules A.

Basal body (base of cilium below cell membrane) consists of 9 microtubule triplets B with no central microtubules.

Axonemal dynein—ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.

Gap junctions enable coordinated ciliary movement.

**Kartagener syndrome**—autosomal recessive dynein arm defect → immotile cilia → dysfunctional ciliated epithelia. Findings: developmental abnormalities due to impaired migration and orientation (eg, situs inversus C, hearing loss due to dysfunctional eustachian tube cilia); recurrent infections (eg, sinusitis, ear infections, bronchiectasis due to impaired ciliary clearance of debris/pathogens); infertility (↑ risk of ectopic pregnancy due to dysfunctional fallopian tube cilia, immotile spermatozoa). Lab findings: ↓ nasal nitric oxide (used as screening test).

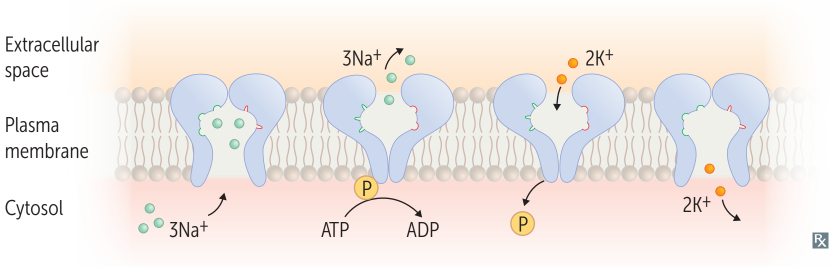



**Sodium-potassium pump**

$Na^+$-$K^+$ ATPase is located in the plasma membrane with ATP site on cytosolic side. For each ATP consumed, **2 $K^+$** go **in** to the cell (pump dephosphorylated) and **3 $Na^+$** go **out** of the cell (pump phosphorylated).

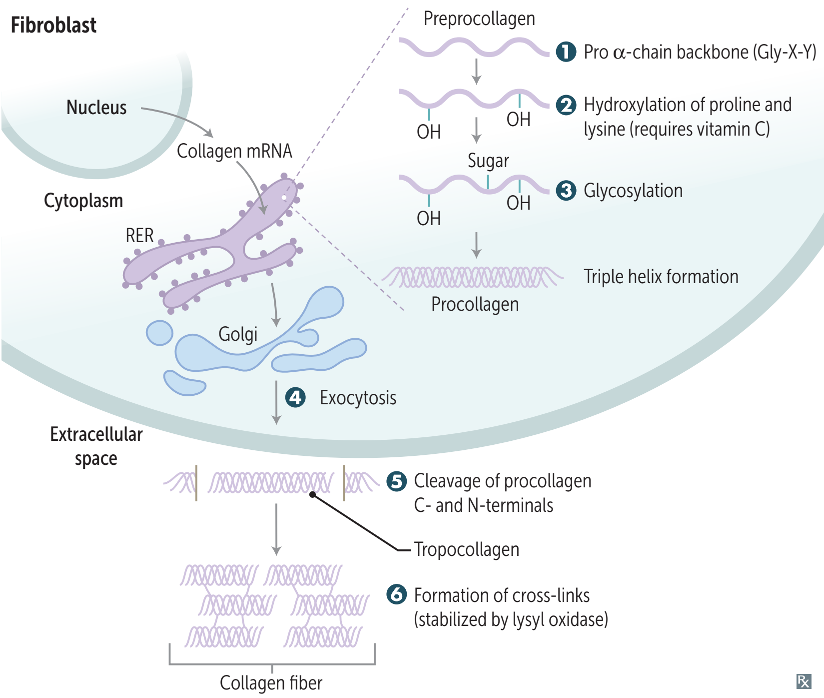
**2** strikes? **K**, you're still **in**. **3** strikes? **Na**h, you're **out**!

Cardiac glycosides (digoxin and digitoxin) directly inhibit $Na^+$-$K^+$ ATPase → indirect inhibition of $Na^+/Ca^{2+}$ exchange → ↑ $[Ca^{2+}]_i$ → ↑ cardiac contractility.



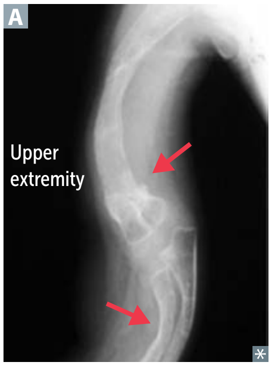
| | | |
|---|---|---|
| **Collagen** | Most abundant protein in the human body.<br>Extensively modified by posttranslational modification.<br>Organizes and strengthens extracellular matrix. | Type I - **S**keleton<br>Type II - **C**artilage<br>Type III - **A**rteries<br>Type IV - **B**asement membrane<br>**SCAB** |
| **Type I** | Most common (90%)—Bone (made by osteoblasts), Skin, Tendon, dentin, fascia, cornea, **late** wound repair. | Type **I**: b**one**, tend**one**.<br>↓ production in osteogenesis imperfecta type I. |
| **Type II** | Cartilage (including hyaline), vitreous body, nucleus pulposus. | Type **II**: car**two**lage. |
| **Type III** | Reticulin—skin, **blood vessels**, uterus, fetal tissue, **early** wound repair. | Type **III**: deficient in **vascular** type of **E**hlers-**D**anlos syndrome (**threE D**). |
| **Type IV** | Basement membrane (basal lamina), lens. | Type **IV**: under the **floor** (basement membrane).<br>Defective in Alport syndrome; targeted by autoantibodies in Goodpasture syndrome. |

## Collagen synthesis and structure




1. **Synthesis**—translation of collagen α chains (preprocollagen)—usually Gly-X-Y (X and Y are proline or lysine). Collagen is ⅓ glycine; glycine content of collagen is less variable than that of lysine and proline. Hydroxyproline is used for lab quantification of collagen.
2. **Hydroxylation**—hydroxylation ("hydrox**C**ylation") of specific proline and lysine residues. Requires vitamin **C**; deficiency → scurvy.
3. **Glycosylation**—glycosylation of pro-α-chain hydroxylysine residues and formation of procollagen via hydrogen and disulfide bonds (triple helix of 3 collagen α chains). Problems forming triple helix → osteogenesis imperfecta.
4. **Exocytosis**—exocytosis of procollagen into extracellular space.
5. **Proteolytic processing**—cleavage of disulfide-rich terminal regions of procollagen → insoluble tropocollagen.
6. **Cross-linking**—reinforcement of many staggered tropocollagen molecules by covalent lysine-hydroxylysine cross-linkage (by copper-containing lysyl oxidase) to make collagen fibrils. Cross-linking of collagen increases with age. Problems with cross-linking → Menkes disease.

## Osteogenesis imperfecta




Genetic bone disorder (brittle bone disease) caused by a variety of gene defects (most commonly *COL1A1* and *COL1A2*).

Most common form is autosomal dominant with ↓ production of otherwise normal type I collagen (altered triple helix formation). Manifestations include:

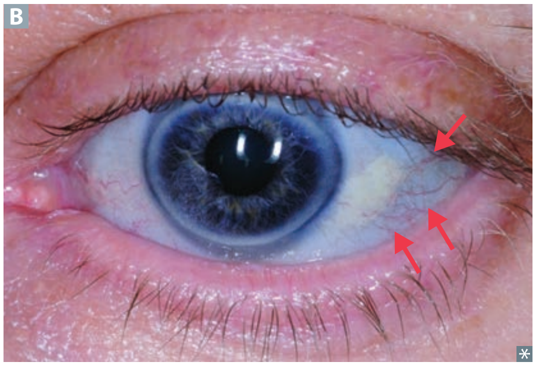
- Multiple fractures and bone deformities (arrows in A) after minimal trauma (eg, during birth)
- Blue sclerae B due to the translucent connective tissue over choroidal veins
- Some forms have tooth abnormalities, including opalescent teeth that wear easily due to lack of dentin (dentinogenesis imperfecta)
- Conductive hearing loss (abnormal ossicles)

May be confused with child abuse.

Treat with bisphosphonates to ↓ fracture risk.

Patients can't **BITE**:

**B**ones = multiple fractures
**I** (eye) = blue sclerae
**T**eeth = dental imperfections
**E**ar = hearing loss




## Ehlers-Danlos syndrome

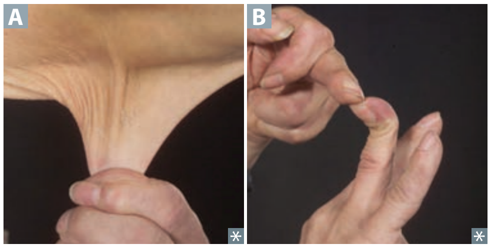
Faulty collagen synthesis causing hyperextensible skin A, hypermobile joints B, and tendency to bleed (easy bruising).

Multiple types. Inheritance and severity vary. Can be autosomal dominant or recessive. May be associated with joint dislocation, berry and aortic aneurysms, organ rupture.

Hypermobility type (joint instability): most common type.

Classical type (joint and skin symptoms): caused by a mutation in type V collagen (eg, *COL5A1*, *COL5A2*).

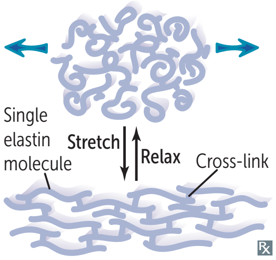
Vascular type (fragile tissues including vessels [eg, aorta], muscles, and organs that are prone to rupture [eg, gravid uterus]): mutations in type III procollagen (eg, *COL3A1*).




## Menkes disease

X-linked recessive connective tissue disease caused by impaired copper absorption and transport due to defective Menkes protein *ATP7A* (**A**bsent copper), vs *ATP7B* in Wilson disease (copper **B**uildup). Leads to ↓ activity of lysyl oxidase (copper is a necessary cofactor) → defective collagen. Results in brittle, "kinky" hair, growth and developmental delay, hypotonia, ↑ risk of cerebral aneurysms.

### Elastin




Stretchy protein within skin, lungs, large arteries, elastic ligaments, vocal cords, epiglottis, ligamenta flava (connect vertebrae → relaxed and stretched conformations).
Rich in nonhydroxylated proline, glycine, and lysine residues, vs the hydroxylated residues of collagen.
Tropoelastin with fibrillin scaffolding.
Cross-linking takes place extracellularly and gives elastin its elastic properties.
Broken down by elastase, which is normally inhibited by $\alpha_1$-antitrypsin.
$\alpha_1$-Antitrypsin deficiency results in unopposed elastase activity, which can cause COPD.
Changes with aging: ↓ dermal collagen and elastin, ↓ synthesis of collagen fibrils; cross-linking remains normal.


**Marfan syndrome**—autosomal dominant (with variable expression) connective tissue disorder affecting skeleton, heart, and eyes. ***FBN1*** gene mutation on chromosome 15 (**f**ifteen) results in defective **f**ibrillin-1, a glycoprotein that forms a sheath around elastin and sequesters TGF-β. Findings: tall with long extremities; chest wall deformity (pectus carinatum [pigeon chest] or pectus excavatum A); hypermobile joints; long, tapering fingers and toes (arachnodactyly); cystic medial necrosis of aorta; aortic root aneurysm rupture or dissection (most common cause of death); mitral valve prolapse; ↑ risk of spontaneous pneumothorax.

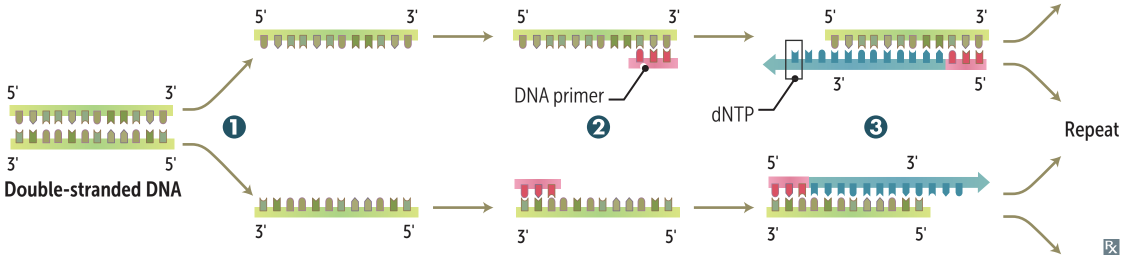
**Homocystinuria**—presentation similar to Marfan syndrome with pectus deformity, tall stature, ↑ arm:height ratio, ↓ upper:lower body segment ratio, arachnodactyly, joint hyperlaxity, skin hyperelasticity, scoliosis.

| | Marfan syndrome | Homocystinuria |
|---|---|---|
| INHERITANCE | Autosomal dominant | Autosomal recessive |
| INTELLECT | Normal | Decreased |
| VASCULAR COMPLICATIONS | Aortic root dilatation | Thrombosis |
| LENS DISLOCATION | Upward (Mar**fan** **fan**s out) | Downward |

## ▸ BIOCHEMISTRY—LABORATORY TECHNIQUES

### Polymerase chain reaction

Molecular biology lab procedure used to amplify a desired fragment of DNA. Useful as a diagnostic tool (eg, neonatal HIV, herpes encephalitis).



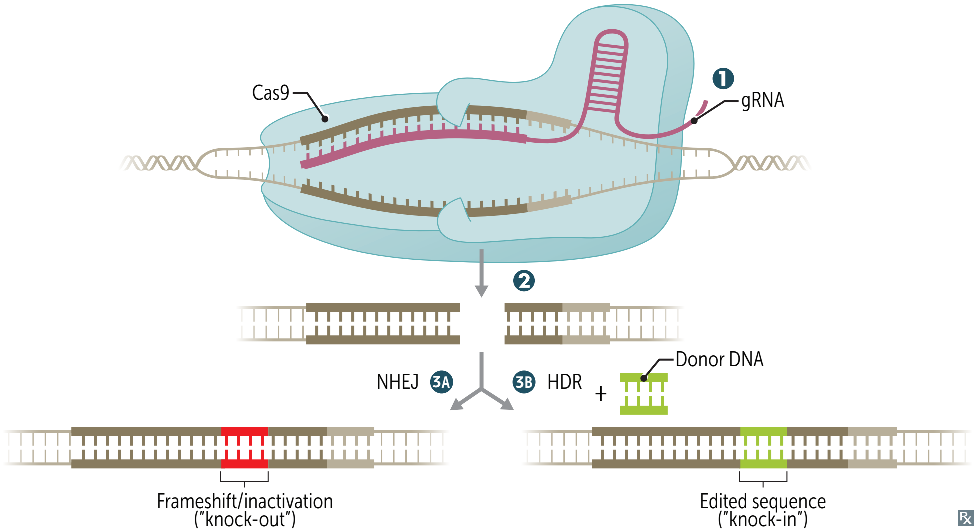

❶ **Denaturation**—DNA is heated to ~95°C to separate the strands.
❷ **Annealing**—Sample is cooled to ~55°C. DNA primers, a heat-stable DNA polymerase *(Taq)*, and deoxynucleotide triphosphates (dNTPs) are added. DNA primers anneal to the specific sequence to be amplified on each strand.
❸ **Elongation**—Temperature is increased to ~72°C. DNA polymerase attaches dNTPs to the strand to replicate the sequence after each primer.

Heating and cooling cycles continue until the amount of DNA is sufficient.

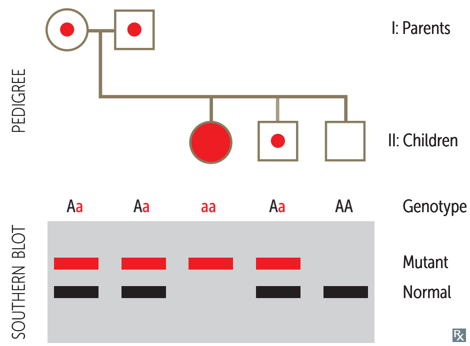
**CRISPR/Cas9**

A genome editing tool derived from bacteria. Consists of a guide RNA (gRNA) ❶, which is complementary to a target DNA sequence, and an endonuclease (Cas9), which makes a single- or double-strand break at the target site ❷. Break imperfectly repaired by nonhomologous end joining (NHEJ) → accidental frameshift mutations ("knock-out") 3A, or a donor DNA sequence can be added to fill in the gap using homology-directed repair (HDR) 3B.

Not used clinically. Potential applications include removing virulence factors from pathogens, replacing disease-causing alleles of genes with healthy variants, and specifically targeting tumor cells.




## Blotting procedures

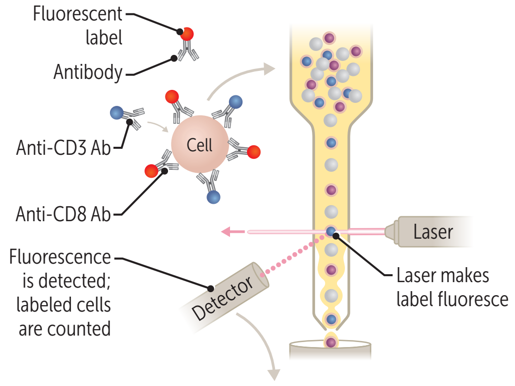
| | | |
|---|---|---|
| **Southern blot** | 1. **DNA** sample is enzymatically cleaved into smaller pieces, which are separated on a gel by electrophoresis, and then transferred to a filter.<br>2. Filter is exposed to radiolabeled DNA probe that recognizes and anneals to its complementary strand.<br>3. Resulting double-stranded, labeled piece of DNA is visualized when filter is exposed to film. |  |
| **Northern blot** | Similar to Southern blot, except that an **RNA** sample is electrophoresed. Useful for studying mRNA levels, which are reflective of gene expression. | **SNoW DRoP**:<br>**S**outhern = **D**NA<br>**N**orthern = **R**NA<br>**W**estern = **P**rotein<br>Northern blots detect splicing errors. |
| **Western blot** | Sample protein is separated via gel electrophoresis and transferred to a membrane. Labeled antibody is used to bind to relevant **protein.** | |
| **Southwestern blot** | Identifies **DNA-binding proteins** (eg, c-Jun, c-Fos [leucine zipper motif]) using labeled double-stranded DNA probes. | |

**Flow cytometry**

Laboratory technique to assess size, granularity, and protein expression (immunophenotype) of individual cells in a sample.

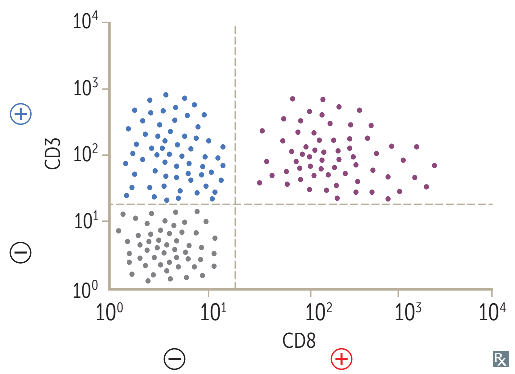
Commonly used in workup of hematologic abnormalities (eg, leukemia, paroxysmal nocturnal hemoglobinuria, fetal RBCs in pregnant person's blood) and immunodeficiencies (eg, $CD4^+$ cell count in HIV).

Cells are tagged with antibodies specific to surface or intracellular proteins. Antibodies are then tagged with a unique fluorescent dye. Sample is analyzed one cell at a time by focusing a laser on the cell and measuring light scatter and intensity of fluorescence.




Data are plotted either as histogram (one measure) or scatter plot (any two measures, as shown). In illustration:

- Cells in left lower quadrant ⊖ for both CD8 and CD3.
- Cells in right lower quadrant ⊕ for CD8 and ⊖ for CD3. In this example, right lower quadrant is empty because all CD8-expressing cells also express CD3.
- Cells in left upper quadrant ⊕ for CD3 and ⊖ for CD8.
- Cells in right upper quadrant ⊕ for both CD8 and CD3.




**Microarrays**

Array consisting of thousands of DNA oligonucleotides arranged in a grid on a glass or silicon chip. The DNA or RNA samples being compared are attached to different fluorophores and hybridized to the array. The ratio of fluorescence signal at a particular oligonucleotide reflects the relative amount of the hybridizing nucleic acid in the two samples.

Used to compare the relative expression of genes in two samples. Can detect single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) for genotyping, clinical genetic testing, forensic analysis, and cancer mutation and genetic linkage analysis.

**Enzyme-linked immunosorbent assay**

Immunologic test used to detect the presence of either a specific antigen or antibody in a patient's blood sample. Detection involves the use of an antibody linked to an enzyme. Added substrate reacts with enzyme, producing a detectable signal. Can have high sensitivity and specificity, but is less specific than Western blot. Often used to screen for HIV infection.

**Karyotyping**

Colchicine is added to cultured cells to halt chromosomes in metaphase. Chromosomes are stained, ordered, and numbered according to morphology, size, arm-length ratio, and banding pattern (arrows in A point to extensive abnormalities in a cancer cell).
Can be performed on a sample of blood, bone marrow, amniotic fluid, or placental tissue.
Used to diagnose chromosomal imbalances (eg, autosomal trisomies, sex chromosome disorders).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**Fluorescence in situ hybridization**

Fluorescent DNA or RNA probe binds to specific gene site of interest on chromosomes (arrows in A point to abnormalities in a cancer cell; each fluorescent color represents a chromosome-specific probe).
Used for specific localization of genes and direct visualization of chromosomal anomalies at the molecular level.

- Microdeletion—no fluorescence on a chromosome compared to fluorescence at the same locus on the second copy of that chromosome.
- Translocation—fluorescence signal that corresponds to one chromosome is found in a different chromosome (two white arrows in A show fragments of chromosome 17 that have translocated to chromosome 19).
- Duplication—a second copy of a chromosome, resulting in a trisomy or tetrasomy (two blue arrows in A duplicated chromosomes 8, resulting in a tetrasomy).


---

**Molecular cloning**

Production of a recombinant DNA molecule in a bacterial host.
Steps:

1. Isolate eukaryotic mRNA (post-RNA processing) of interest.
2. Add reverse transcriptase (an RNA-dependent DNA polymerase) to produce complementary DNA (cDNA, lacks introns).
3. Insert cDNA fragments into bacterial plasmids containing antibiotic resistance genes.
4. Transform (insert) recombinant plasmid into bacteria.
5. Surviving bacteria on antibiotic medium produce cloned DNA (copies of cDNA).

| | | |
|---|---|---|
| **Gene expression modifications** | Transgenic strategies in mice involve:<br>▪ Random insertion of gene into mouse genome<br>▪ Targeted insertion or deletion of gene through homologous recombination with mouse gene | Knock-**out** = removing a gene, taking it **out**.<br>Knock-**in** = **in**serting a gene.<br><br>Random insertion—constitutive expression.<br>Targeted insertion—conditional expression. |
| **RNA interference** | Process whereby small non-coding RNA molecules target mRNAs to inhibit gene expression. | |
| MicroRNA | Naturally produced by cell as hairpin structures. Loose nucleotide pairing allows broad targeting of related mRNAs. When miRNA binds to mRNA, it blocks translation of mRNA and sometimes facilitates its degradation. | Abnormal expression of miRNAs contributes to certain malignancies (eg, by silencing an mRNA from a tumor suppressor gene). |
| Small interfering RNA | Usually derived from exogenous dsRNA source (eg, virus). Once inside a cell, siRNA requires complete nucleotide pairing, leading to highly specific mRNA targeting. Results in mRNA cleavage prior to translation. | Can be produced by in vitro transcription for gene "knockdown" experiments. |

## ▸ BIOCHEMISTRY—GENETICS

### Genetic terms

| TERM | DEFINITION | EXAMPLE |
|---|---|---|
| **Codominance** | Both alleles contribute to the phenotype of the heterozygote. | Blood groups A, B, AB; $\alpha_1$-antitrypsin deficiency; HLA groups. |
| **Variable expressivity** | Patients with the same genotype have varying phenotypes. | 2 patients with neurofibromatosis type 1 (NF1) may have varying disease severity. |
| **Incomplete penetrance** | Not all individuals with a mutant genotype show the mutant phenotype.<br>% penetrance × probability of inheriting genotype = risk of expressing phenotype. | *BRCA1* gene mutations do not always result in breast or ovarian cancer. |
| **Pleiotropy** | One gene contributes to multiple phenotypic effects. | Untreated phenylketonuria (PKU) manifests with light skin, intellectual disability, and musty body odor. |
| **Anticipation** | Increased severity or earlier onset of disease in succeeding generations. | Trinucleotide repeat diseases (eg, Huntington disease). |
| **Loss of heterozygosity** | If a patient inherits or develops a mutation in a tumor suppressor gene, the wild type allele must be deleted/mutated before cancer develops. This is not true of oncogenes. | Retinoblastoma and the "two-hit hypothesis," Lynch syndrome (HNPCC), Li-Fraumeni syndrome. |

### Genetic terms *(continued)*

| TERM | DEFINITION | EXAMPLE |
|---|---|---|
| **Dominant negative mutation** | Exerts a dominant effect. A heterozygote produces a nonfunctional altered protein that also prevents the normal gene product from functioning. | A single mutated *p53* tumor suppressor gene results in a protein that is able to bind DNA and block the nonmutated p53 from binding to the promoter. |
| **Linkage disequilibrium** | Tendency for certain alleles at 2 linked loci to occur together more or less often than expected by chance. Measured in a population, not in a family, and often varies in different populations. | |
| **Mosaicism**  | Presence of genetically distinct cell lines in the same individual.<br>Somatic mosaicism—mutation arises from mitotic errors after fertilization and propagates through multiple tissues or organs.<br>Gonadal mosaicism—mutation only in egg or sperm cells. If parents and relatives do not have the disease, suspect gonadal (or germline) mosaicism. | **McCune-Albright syndrome**—due to $G_s$-protein activating mutation. Presents with unilateral café-au-lait spots A with ragged edges, polyostotic fibrous dysplasia (bone is replaced by collagen and fibroblasts), and at least one endocrinopathy (eg, precocious puberty). Lethal if mutation occurs before fertilization (affecting all cells), but survivable in patients with mosaicism. |
| **Locus heterogeneity** | Mutations at different loci can produce a similar phenotype. | Albinism, retinitis pigmentosa, familial hypercholesteremia. |
| **Allelic heterogeneity** | Different mutations in the same locus produce the same phenotype. | β-thalassemia. |
| **Heteroplasmy** | Presence of both normal and mutated mtDNA, resulting in variable expression in mitochondrially inherited disease. | mtDNA passed from mother to all children. |
| **Uniparental disomy** | Offspring receives 2 copies of a chromosome from 1 parent and no copies from the other parent. HeterodIsomy (heterozygous) indicates a meiosis I error. IsodIsomy (homozygous) indicates a meiosis II error or postzygotic chromosomal duplication of one of a pair of chromosomes, and loss of the other of the original pair. | Uniparental is euploid (correct number of chromosomes). Most occurrences of uniparental disomy (UPD) → normal phenotype. Consider isodisomy in an individual manifesting a recessive disorder when only one parent is a carrier. Examples: Prader-Willi and Angelman syndromes. |

### Hardy-Weinberg population genetics

| | A (p) | a (q) |
|---|---|---|
| A (p) | AA ($p^2$) | Aa (pq) |
| a (q) | Aa (pq) | aa ($q^2$) |

If p and q represent the frequencies of alleles A and a, respectively, in a population, then $p + q = 1$:
- $p^2$ = frequency of homozygosity for allele A
- $q^2$ = frequency of homozygosity for allele a
- $2pq$ = frequency of heterozygosity (carrier frequency, if an autosomal recessive disease)

Therefore, the sum of the frequencies of these genotypes is $p^2 + 2pq + q^2 = 1$.

The frequency of an X-linked recessive disease in males = q and in females = $q^2$.

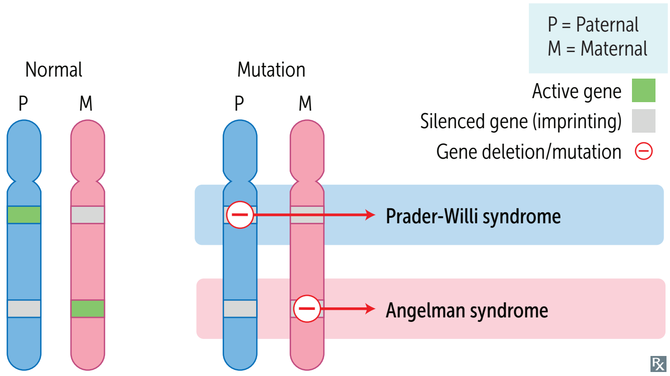
Hardy-Weinberg law assumptions include:
- No mutation occurring at the locus
- Natural selection is not occurring
- Completely random mating
- No net migration
- Large population

If a population is in Hardy-Weinberg equilibrium, then the values of p and q remain constant from generation to generation.

## Disorders of imprinting

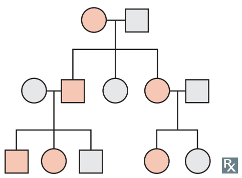
Imprinting—one gene copy is silenced by methylation, and only the other copy is expressed → parent-of-origin effects.

| | Prader-Willi syndrome | Angelman syndrome |
|---|---|---|
| WHICH GENE IS SILENT? | Maternally derived genes are silenced<br>Disease occurs when the **p**aternal allele is deleted or mutated | Paternally derived *UBE3A* is silenced<br>Disease occurs when the **m**aternal allele is deleted or mutated |
| SIGNS AND SYMPTOMS | Hyperphagia, obesity, intellectual disability, hypogonadism, hypotonia | **S**eizures, **A**taxia, severe **I**ntellectual disability, inappropriate **L**aughter<br>Set **SAIL** for Angel Island |
| CHROMOSOMES INVOLVED | Chromosome 15 of paternal origin | *UBE3A* on maternal copy of chromosome 15 |
| NOTES | 25% of cases are due to maternal uniparental disomy | 5% of cases are due to paternal uniparental disomy |
| | **POP**: **P**rader-Willi, **O**besity/overeating, **P**aternal allele deleted | **MAMAS**: **M**aternal allele deleted, **A**ngelman syndrome, **M**ood, **A**taxia, **S**eizures |



## Modes of inheritance

### Autosomal dominant

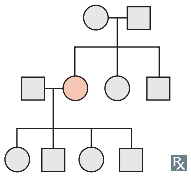


Often due to defects in structural genes. Many generations, both males and females are affected.

| | A | a |
|---|---|---|
| a | Aa | aa |
| a | Aa | aa |

Often pleiotropic (multiple apparently unrelated effects) and variably expressive (different between individuals). Family history crucial to diagnosis. With one affected (heterozygous) parent, on average, ½ of children affected.

### Autosomal recessive



With 2 carrier (heterozygous) parents, on average: ¼ of children will be affected (homozygous), ½ of children will be carriers, and ¼ of children will be neither affected nor carriers.

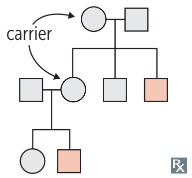
| | A | a |
|---|---|---|
| A | AA | Aa |
| a | Aa | aa |

Often due to enzyme deficiencies. Usually seen in only 1 generation. Commonly more severe than dominant disorders; patients often present in childhood.

↑ risk in consanguineous families.

Unaffected individual with affected sibling has 2/3 probability of being a carrier.

### X-linked recessive



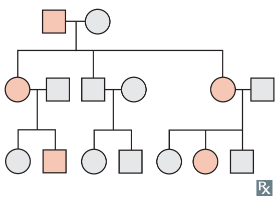

Sons of heterozygous mothers have a 50% chance of being affected. No male-to-male transmission. Skips generations.

| | X | X |
|---|---|---|
| X | XX | XX |
| Y | XY | XY |

| | X | X |
|---|---|---|
| X | XX | XX |
| Y | XY | XY |

Commonly more severe in males. Females usually must be homozygous to be affected.

### X-linked dominant



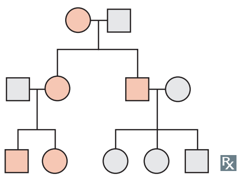
Transmitted through both parents. Mothers transmit to 50% of daughters and sons; fathers transmit to all daughters but no sons.

| | X | X |
|---|---|---|
| X | XX | XX |
| Y | XY | XY |

| | X | X |
|---|---|---|
| X | XX | XX |
| Y | XY | XY |

Examples: fragile X syndrome, Alport syndrome, **hypophosphatemic rickets** (also called X-linked hypophosphatemia)—phosphate wasting at proximal tubule → rickets-like presentation.

### Mitochondrial inheritance



Transmitted only through the mother. All offspring of affected females may show signs of disease.

Variable expression in a population or even within a family due to heteroplasmy.

**Mitochondrial myopathies**—rare disorders; often present with myopathy, lactic acidosis, and CNS disease, eg, MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). 2° to failure in oxidative phosphorylation. Muscle biopsy often shows "ragged red fibers" (due to accumulation of diseased mitochondria in the subsarcolemma of the muscle fiber).

**Leber hereditary optic neuropathy** (LHON)—cell death in optic nerve neurons → subacute bilateral vision loss in teens/young adults, 90% males. Usually permanent. Also leads to neurologic dysfunction, cardiac conduction defects.

= unaffected male; = affected male; = unaffected female; = affected female.

**Autosomal dominant diseases**

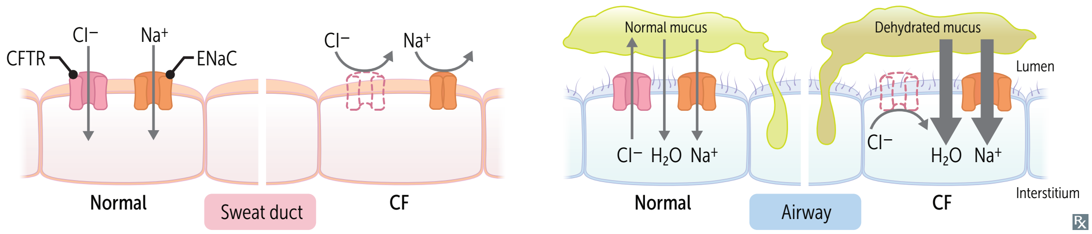
Achondroplasia, autosomal dominant polycystic kidney disease, familial adenomatous polyposis, familial hypercholesterolemia, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), hereditary spherocytosis, Huntington disease, Li-Fraumeni syndrome, Marfan syndrome, multiple endocrine neoplasias, myotonic muscular dystrophy, neurofibromatosis type 1 (von Recklinghausen disease), neurofibromatosis type 2, tuberous sclerosis, von Hippel-Lindau disease.

**Autosomal recessive diseases**

Oculocutaneous albinism, phenylketonuria, cystic fibrosis, sickle cell disease, Wilson disease, sphingolipidoses (except Fabry disease), hemochromatosis, glycogen storage diseases, thalassemia, mucopolysaccharidoses (except Hunter syndrome), Friedreich ataxia, Kartagener syndrome, ARPKD. Oh please! Can students who score high grades tell me features of the kidney disorder Autosomal Recessive Polycystic Kidney Disease?

## Cystic fibrosis

| | |
|---|---|
| GENETICS | Autosomal recessive; defect in *CFTR* gene on chromosome 7; commonly a deletion of Phe508. Most common lethal genetic disease in patients with European ancestry. |
| PATHOPHYSIOLOGY | *CFTR* encodes an ATP-gated $Cl^-$ channel that secretes $Cl^-$ in lungs and GI tract, and reabsorbs $Cl^-$ in sweat glands. Phe508 deletion → misfolded protein → improper protein trafficking and protein retention in RER → protein absent from cell membrane → ↓ $Cl^-$ (and $H_2O$) secretion; ↑ intracellular $Cl^-$ results in compensatory ↑ $Na^+$ reabsorption via epithelial $Na^+$ channels (ENaC) → ↑ $H_2O$ reabsorption → abnormally thick mucus secreted into lungs and GI tract. ↑ $Na^+$ reabsorption also causes more negative transepithelial potential difference. |
| DIAGNOSIS | ↑ $Cl^-$ concentration in pilocarpine-induced sweat test is diagnostic. Can present with contraction alkalosis and hypokalemia (ECF effects analogous to a patient taking a loop diuretic) because of ECF $H_2O/Na^+$ losses via sweating and concomitant renal $K^+/H^+$ wasting. ↑ immunoreactive trypsinogen (newborn screening) due to clogging of pancreatic duct. |
| COMPLICATIONS | Recurrent pulmonary infections (eg, *S aureus* [infancy and early childhood], *P aeruginosa* [adulthood], allergic bronchopulmonary aspergillosis [ABPA]), chronic bronchitis and bronchiectasis → reticulonodular pattern on CXR, opacification of sinuses. Nasal polyps, nail clubbing.<br>Pancreatic insufficiency, malabsorption with steatorrhea, and fat-soluble vitamin deficiencies (A, D, E, K) progressing to endocrine dysfunction (CF-related diabetes), biliary cirrhosis, liver disease. Meconium ileus in newborns.<br>Infertility in males (absence of vas deferens, spermatogenesis may be unaffected) and subfertility in females (amenorrhea, abnormally thick cervical mucus). |
| TREATMENT | Multifactorial: chest physiotherapy, albuterol, aerosolized dornase alfa (DNase), and inhaled hypertonic saline facilitate mucus clearance. Azithromycin used as anti-inflammatory agent. Ibuprofen slows disease progression. Pancreatic enzyme replacement therapy (pancrelipase) for pancreatic insufficiency.<br>Combination of lumacaftor or tezacaftor (each corrects misfolded proteins and improves their transport to cell surface) with ivacaftor. (opens $Cl^-$ channels → improved chloride transport). |



### X-linked recessive diseases

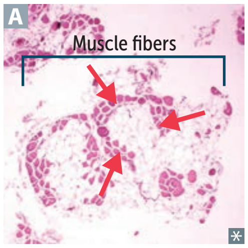
Bruton agammaglobulinemia, Duchenne and Becker muscular dystrophies, Fabry disease, G6PD deficiency, hemophilia A and B, Hunter syndrome, Lesch-Nyhan syndrome, ocular albinism, ornithine transcarbamylase deficiency, Wiskott-Aldrich syndrome.

Females with Turner syndrome (45,XO) are more likely to have an X-linked recessive disorder.

X-inactivation (lyonization)—during development, one of the X chromosomes in each XX cell is randomly deactivated and condensed into a Barr body (methylated heterochromatin). If skewed inactivation occurs, XX individuals may express X-linked recessive diseases (eg, G6PD); penetrance and severity of X-linked dominant diseases in XX individuals may also be impacted.

## Muscular dystrophies

### Duchenne




X-linked recessive disorder typically due to **frameshift** deletions or nonsense mutations → truncated or absent dystrophin protein → progressive myofiber damage. Weakness begins in pelvic girdle muscles and progresses superiorly. Pseudohypertrophy of calf muscles due to fibrofatty replacement of muscle A. Waddling gait.

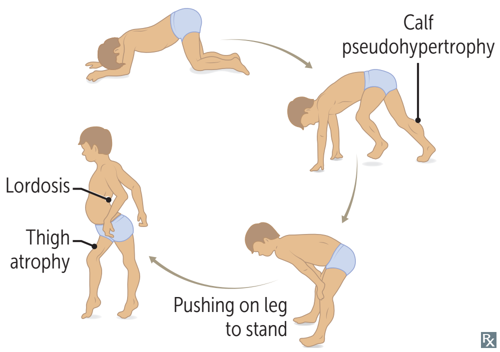
Onset before 5 years of age. Dilated cardiomyopathy is common cause of death.

Gowers sign—patient uses upper extremities to help stand up. Classically seen in Duchenne muscular dystrophy, but also seen in other muscular dystrophies and inflammatory myopathies (eg, polymyositis).

Duchenne = deleted dystrophin.

Dystrophin gene (*DMD*) is the largest protein-coding human gene → ↑ chance of spontaneous mutation. Dystrophin helps anchor muscle fibers, primarily in skeletal and cardiac muscle. It connects the intracellular cytoskeleton (actin) to the transmembrane proteins α- and β-dystroglycan, which are connected to the extracellular matrix (ECM). Loss of dystrophin → myonecrosis.

↑ CK and aldolase; genetic testing confirms diagnosis.




### Becker

X-linked recessive disorder typically due to **non-frameshift** deletions in dystrophin gene (partially functional instead of truncated). Less severe than Duchenne (Becker is better). Onset in adolescence or early adulthood.

Deletions can cause both Duchenne and Becker muscular dystrophies. ⅔ of cases have large deletions spanning one or more exons.

### Myotonic dystrophy

Autosomal dominant. Onset 20–30 years. CTG trinucleotide repeat expansion in the *DMPK* gene → abnormal expression of myotonin protein kinase → myotonia (eg, difficulty releasing hand from handshake), muscle wasting, cataracts, testicular atrophy, frontal balding, arrhythmia.

Cataracts, Toupee (early balding in males), Gonadal atrophy.

**Rett syndrome**

Sporadic disorder seen almost exclusively in females (affected males die in utero or shortly after birth). Most cases are caused by de novo mutation of *MECP2* on X chromosome. Symptoms of **Rett** syndrome usually appear between ages 1–4 and are characterized by regression ("**rett**urn") in motor, verbal, and cognitive abilities; ataxia; seizures; growth deceleration; and stereotyped hand-wringing.

**Fragile X syndrome**

X-linked dominant inheritance. Trinucleotide repeats in FMR1 → hypermethylation of cytosine residues → ↓ expression.

Most common inherited cause of intellectual disability (Down syndrome is most common genetic cause, but most cases occur sporadically).

Trinucleotide repeat expansion [$(CGG)_n$] occurs during oogenesis.

Premutation (50-200 repeats) → tremor, ataxia, 1° ovarian insufficiency.

Full mutation (>200 repeats) → postpubertal macroorchidism (enlarged testes), long face with large jaw, large everted ears, autism, mitral valve prolapse, hypermobile joints.

Self-mutilation is common and can be confused with Lesch-Nyhan syndrome.

**Trinucleotide repeat expansion diseases**

May show genetic anticipation (disease severity ↑ and age of onset ↓ in successive generations).

| DISEASE | TRINUCLEOTIDE REPEAT | MODE OF INHERITANCE | MNEMONIC |
|---|---|---|---|
| **Huntington disease** | $(CAG)_n$ | AD | **C**audate has ↓ **A**Ch and **G**ABA |
| **Myotonic dystrophy** | $(CTG)_n$ | AD | **C**ataracts, **T**oupee (early balding in males), **G**onadal atrophy in males, reduced fertility in females |
| **Fragile X syndrome** | $(CGG)_n$ | XD | **C**hin (protruding), **G**iant **G**onads |
| **Friedreich ataxia** | $(GAA)_n$ | AR | Ataxic **GAA**it |

## Autosomal trisomies

Autosomal monosomies are incompatible with life due to a high chance of expression of recessive traits for that chromosome.

### Down syndrome (trisomy 21)

Single palmar crease

Findings: intellectual disability, flat facies, prominent epicanthal folds, single palmar crease, incurved 5th finger, gap between 1st 2 toes, duodenal atresia, Hirschsprung disease, congenital heart disease (eg, ASD), Brushfield spots (whitish spots at the periphery of the iris). Associated with early-onset Alzheimer disease (chromosome 21 codes for amyloid precursor protein), ↑ risk of AML/ALL.

95% of cases due to meiotic nondisjunction, most commonly during meiosis I (↑ with advanced maternal age: from 1:1500 in females < 20 to 1:25 in females > 45).

4% of cases due to unbalanced Robertsonian translocation, most typically between chromosomes 14 and 21. Only 1% of cases are due to postfertilization mitotic error.

Incidence 1:700.

**D**rinking age (**21**).

Most common viable chromosomal disorder and most common cause of genetic intellectual disability.

First-trimester ultrasound commonly shows ↑ nuchal translucency and hypoplastic nasal bone. Markers for Down syndrome are **hi** up: ↑ **h**CG, ↑ **i**nhibin.

The **5 A**'s of Down syndrome:

- **A**dvanced maternal age
- **A**tresia (duodenal)
- **A**trioventricular septal defect
- **A**lzheimer disease (early onset)
- **A**ML/**A**LL

### Edwards syndrome (trisomy 18)

Findings: **PRINCE** Edward—**P**rominent occiput, **R**ocker-bottom feet, **I**ntellectual disability, **N**ondisjunction, **C**lenched fists with overlapping fingers, low-set **E**ars, micrognathia (small jaw), congenital heart disease, omphalocele, myelomeningocele. Death usually occurs by age 1.

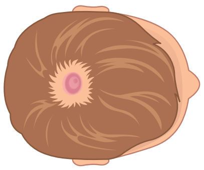
Incidence 1:8000.

**E**lection age (**18**).

2nd most common autosomal trisomy resulting in live birth (most common is Down syndrome).

In **Ed**wards syndrome, **e**very prenatal screening marker **d**ecreases.

### Patau syndrome (trisomy 13)



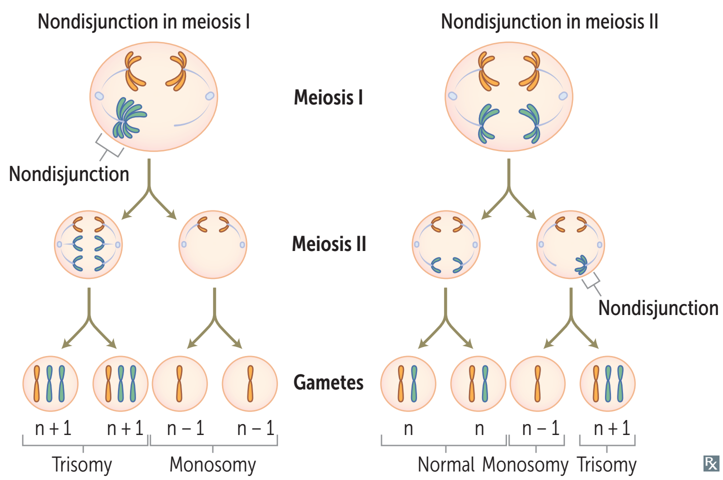
Cutis aplasia

Findings: severe intellectual disability, rocker-bottom feet, microphthalmia, microcephaly, cleft li**p**/**p**alate, holo**p**rosencephaly, **p**olydactyly, cutis a**p**lasia, congenital heart (**p**ump) disease, **p**olycystic kidney disease, omphalocele. Death usually occurs by age 1.

Incidence 1:15,000.

**P**uberty at age **13**.

Defect in fusion of prechordal mesoderm → midline defects.




| 1st trimester screening | | |
|---|---|---|
| **Trisomy** | **β-hCG** | **PAPP-A** |
| 21 | ↑ | ↓ |
| 18 | ↓ | ↓ |
| 13 | ↓ | ↓ |

| 2nd trimester screening | | | | |
|---|---|---|---|---|
| **Trisomy** | **β-hCG** | **Inhibin A** | **Estriol** | **AFP** |
| 21 | ↑ | ↑ | ↓ | ↓ |
| 18 | ↓ | — or ↓ | ↓ | ↓ |
| 13 | — | — | — | — |

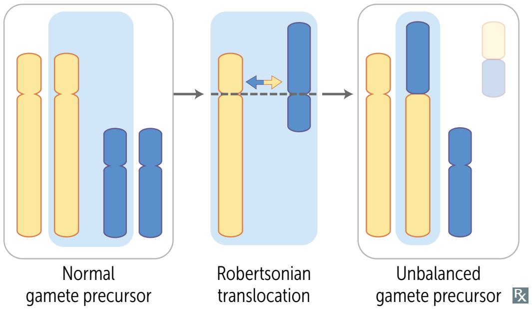
### Genetic disorders by chromosome

| CHROMOSOME | SELECTED EXAMPLES |
|---|---|
| 3 | von Hippel-Lindau disease, renal cell carcinoma |
| 4 | ADPKD (*PKD2*), achondroplasia, Huntington disease |
| 5 | Cri-du-chat syndrome, familial adenomatous polyposis |
| 6 | Hemochromatosis (*HFE*) |
| 7 | Williams syndrome, cystic fibrosis |
| 9 | Friedreich ataxia, tuberous sclerosis (*TSC1*) |
| 11 | Wilms tumor, β-globin gene defects (eg, sickle cell disease, β-thalassemia), MEN1 |
| 13 | Patau syndrome, Wilson disease, retinoblastoma (*RB1*), *BRCA2* |
| 15 | Prader-Willi syndrome, Angelman syndrome, Marfan syndrome |
| 16 | ADPKD (*PKD1*), α-globin gene defects (eg, α-thalassemia), tuberous sclerosis (*TSC2*) |
| 17 | Neurofibromatosis type 1, *BRCA1*, *TP53* (Li-Fraumeni syndrome) |
| 18 | Edwards syndrome |
| 21 | Down syndrome |
| 22 | Neurofibromatosis type 2, DiGeorge syndrome (22q11) |
| X | Fragile X syndrome, X-linked agammaglobulinemia, Klinefelter syndrome (XXY) |

### Robertsonian translocation

Chromosomal translocation that commonly involves chromosome pairs 21, 22, 13, 14, and 15. One of the most common types of translocation. Occurs when the long arms of 2 acrocentric chromosomes (chromosomes with centromeres near their ends) fuse at the centromere and the 2 short arms are lost.

Balanced translocations (no gain or loss of significant genetic material) normally do not cause abnormal phenotype. Unbalanced translocations (missing or extra genes) can result in miscarriage, stillbirth, and chromosomal imbalance (eg, Down syndrome, Patau syndrome).




### Cri-du-chat syndrome

*Cri du chat* = cry of the cat. Congenital deletion on short arm of chromosome 5 (46,XX or XY, 5p–).

Findings: microcephaly, moderate to severe intellectual disability, high-pitched **cry**ing, epicanthal folds, cardiac abnormalities (VSD).

### Williams syndrome

Congenital microdeletion of long arm of chromosome 7 (deleted region includes elastin gene).

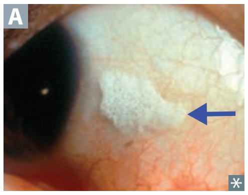
Findings: distinctive "elfin" facies, intellectual disability, hypercalcemia, well-developed verbal skills, extreme friendliness with strangers, cardiovascular problems (eg, supravalvular aortic stenosis, renal artery stenosis).

## ▸ BIOCHEMISTRY—NUTRITION

| | | |
|---|---|---|
| **Essential fatty acids** | Polyunsaturated fatty acids that cannot be synthesized in the body and must be provided in the diet (eg, nuts and seeds, plant oils, seafood). Linoleic acid (omega-6) is metabolized to arachidonic acid, which serves as the precursor to leukotrienes and prostaglandins. Linolenic acid (omega-3) and its metabolites have cardioprotective and antihyperlipidemic effects. | |
| **Vitamins: fat soluble** | A, D, E, K. Absorption dependent on ileum and pancreas. Toxicity more common than for water-soluble vitamins because fat-soluble vitamins accumulate in fat. | Malabsorption syndromes with steatorrhea (eg, cystic fibrosis and celiac disease) or mineral oil intake can cause fat-soluble vitamin deficiencies. |
| **Vitamins: water soluble** | $B_1$ (thiamine: TPP)<br>$B_2$ (riboflavin: FAD, FMN)<br>$B_3$ (niacin: $NAD^+$)<br>$B_5$ (pantothenic acid: CoA)<br>$B_6$ (pyridoxine: PLP)<br>$B_7$ (biotin)<br>$B_9$ (folate)<br>$B_{12}$ (cobalamin)<br>C (ascorbic acid) | Wash out easily from body except $B_{12}$ and $B_9$. $B_{12}$ stored in liver for ~ 3–4 years. $B_9$ stored in liver for ~ 3–4 months.<br>B-complex deficiencies often result in dermatitis, glossitis, and diarrhea.<br>Can be coenzymes (eg, ascorbic acid) or precursors to coenzymes (eg, FAD, $NAD^+$). |

## Vitamin A

Includes retinal, retinol, retinoic acid.

| | | |
|---|---|---|
| FUNCTION | Antioxidant; constituent of visual pigments (**retinal**); essential for normal differentiation of epithelial cells into specialized tissue (pancreatic cells, mucus-secreting cells); prevents squamous metaplasia. | **Retin**ol is vitamin **A**, so think **retin-A** (used topically for wrinkles and **A**cne). Found in liver and leafy vegetables. Supplementation in vitamin A-deficient measles patients may improve outcomes. Use oral isotretinoin to treat severe cystic acne. Use *all*-trans retinoic acid to treat acute promyelocytic leukemia. |
| DEFICIENCY  | Night blindness (nyctalopia); dry, scaly skin (xerosis cutis); dry eyes (xerophthalmia); corneal squamous metaplasia → Bitot spots (keratin debris; foamy appearance on conjunctiva A); corneal degeneration (keratomalacia); immunosuppression. | |
| EXCESS | Acute toxicity—nausea, vomiting, ↑ ICP (eg, vertigo, blurred vision). Chronic toxicity—alopecia, dry skin (eg, scaliness), hepatic toxicity and enlargement, arthralgias, and idiopathic intracranial hypertension. | Teratogenic (cleft palate, cardiac abnormalities), therefore a ⊖ pregnancy test and two forms of contraception are required before isotretinoin (vitamin A derivative) is prescribed. **Is**o**tret**inoin **is terat**ogenic. |

## Vitamin $B_1$

Also called thiamine.

**FUNCTION**

In thiamine pyrophosphate (TPP), a cofactor for several dehydrogenase enzyme reactions (**Be APT**):
- **B**ranched-chain ketoacid dehydrogenase
- **α**-Ketoglutarate dehydrogenase (TCA cycle)
- **P**yruvate dehydrogenase (links glycolysis to TCA cycle)
- **T**ransketolase (HMP shunt)

**DEFICIENCY**

Impaired glucose breakdown → ATP depletion worsened by glucose infusion; highly aerobic tissues (eg, brain, heart) are affected first. In patients with chronic alcohol overuse or malnutrition, give thiamine before dextrose to ↓ risk of precipitating Wernicke encephalopathy.
Diagnosis made by ↑ in RBC transketolase activity following vitamin $B_1$ administration.

| DISORDER | CHARACTERISTICS | |
|---|---|---|
| **Wernicke encephalopathy** | Acute, reversible, life-threatening neurologic condition. Symptoms: **C**onfusion, **O**phthalmoplegia/**N**ystagmus, **A**taxia (**C**or**ONA** beer). | |
| **Korsakoff syndrome** | Amnestic disorder due to chronic alcohol overuse; presents with confabulation, personality changes, memory loss (permanent). | |
| **Wernicke-Korsakoff syndrome** | Damage to medial dorsal nucleus of thalamus, mammillary bodies. Presentation is combination of Wernicke encephalopathy and Korsakoff syndrome. | |
| **Dry beriberi** | Polyneuropathy, symmetric muscle wasting. | Spell beriberi as **Ber1Ber1** to remember vitamin **$B_1$**. |
| **Wet beriberi** | High-output cardiac failure (dilated cardiomyopathy), edema. | |

## Vitamin $B_2$

Also called riboflavin.

| | | |
|---|---|---|
| FUNCTION | Component of flavins FAD and FMN, used as cofactors in redox reactions, eg, the succinate dehydrogenase reaction in the TCA cycle. | **F**AD and **F**MN are derived from ribo**F**lavin ($B_2 \approx$ **2** ATP). |
| DEFICIENCY | **C**heilosis (inflammation of lips, scaling and fissures at the corners of the mouth), "magenta" tongue, **c**orneal vascularization. | The **2 C**'s of $B_2$. |

## Vitamin $B_3$

Also called niacin, nicotinic acid.

| | | |
|---|---|---|
| FUNCTION | Constituent of $NAD^+$, $NADP^+$ (used in redox reactions and as cofactor by dehydrogenases). Derived from tryptophan. Synthesis requires vitamins $B_2$ and $B_6$. Used to treat dyslipidemia (↓ VLDL, ↑ HDL). | **N**AD derived from **N**iacin ($B_3 \approx$ **3** ATP). |
| DEFICIENCY  | Glossitis. Severe deficiency of $B_3$ leads to pellagra, which can also be caused by Hartnup disease, malignant carcinoid syndrome (↑ tryptophan metabolism → ↑ serotonin synthesis), and isoniazid (↓ vitamin $B_6$). Symptoms of $B_3$ deficiency (pellagra) (the **3 D**'s): **d**iarrhea, **d**ementia (also hallucinations), **d**ermatitis (C3/C4 dermatome circumferential "broad collar" rash [Casal necklace], hyperpigmentation of sun-exposed limbs A). | **Hartnup disease**—autosomal recessive. Deficiency of neutral amino acid (eg, tryptophan) transporters in proximal renal tubular cells and on enterocytes → neutral aminoaciduria and ↓ absorption from the gut → ↓ tryptophan for conversion to niacin → pellagra-like symptoms. Treat with high-protein diet and nicotinic acid. Deficiency of vitamin $B_3$ → pel**l**agra. **L**ess $B_3$. |
| EXCESS | Facial flushing (induced by prostaglandin, not histamine; can avoid by taking aspirin with niacin), hyperglycemia, hyperuricemia. | Excess of vitamin $B_3$ → po**d**agra (gout). **O**ver**d**ose (excess) $B_3$. |

## Vitamin $B_5$

Also called pantothenic acid. $B_5$ is "**pento**"thenic acid.

| | |
|---|---|
| FUNCTION | Component of coenzyme A (CoA, a cofactor for acyl transfers) and fatty acid synthase. |
| DEFICIENCY | Dermatitis, enteritis, alopecia, adrenal insufficiency may lead to burning sensation of feet ("burning feet syndrome"; distal paresthesias, dysesthesia). |

## Vitamin $B_6$

Also called pyridoxine.

| | |
|---|---|
| FUNCTION | Converted to pyridoxal phosphate (PLP), a cofactor used in transamination (eg, ALT and AST), decarboxylation reactions, glycogen phosphorylase. Synthesis of glutathione, cystathionine, heme, niacin, histamine, and neurotransmitters including serotonin, epinephrine, norepinephrine (NE), dopamine, and GABA. |
| DEFICIENCY | Convulsions, hyperirritability, peripheral neuropathy (deficiency inducible by isoniazid and oral contraceptives), sideroblastic anemia (due to impaired hemoglobin synthesis and iron excess). |

## Vitamin $B_7$

Also called biotin.

**FUNCTION**

Cofactor for carboxylation enzymes (which add a 1-carbon group):
- Pyruvate carboxylase (gluconeogenesis): pyruvate (3C) → oxaloacetate (4C)
- Acetyl-CoA carboxylase (fatty acid synthesis): acetyl-CoA (2C) → malonyl-CoA (3C)
- Propionyl-CoA carboxylase (fatty acid oxidation): propionyl-CoA (3C) → methylmalonyl-CoA (4C)

**DEFICIENCY**

Relatively rare. Dermatitis, enteritis, alopecia. Caused by long-term antibiotic use or excessive ingestion of raw egg whites.

"**Avid**in in egg whites **avid**ly binds biotin."

## Vitamin $B_9$

Also called folate.

**FUNCTION**

Converted to tetrahydrofolic acid (THF), a coenzyme for 1-carbon transfer/methylation reactions.

Important for the synthesis of nitrogenous bases in DNA and RNA.

Found in leafy green vegetables. Also produced by gut flora. Absorbed in jejunum. **Fol**ate from **fol**iage.

Small reserve pool stored primarily in the liver.

**DEFICIENCY**

Macrocytic, megaloblastic anemia; hypersegmented polymorphonuclear cells (PMNs); glossitis; no neurologic symptoms (as opposed to vitamin $B_{12}$ deficiency).

Labs: ↑ homocysteine, normal methylmalonic acid levels. Seen in chronic alcohol overuse and in pregnancy.

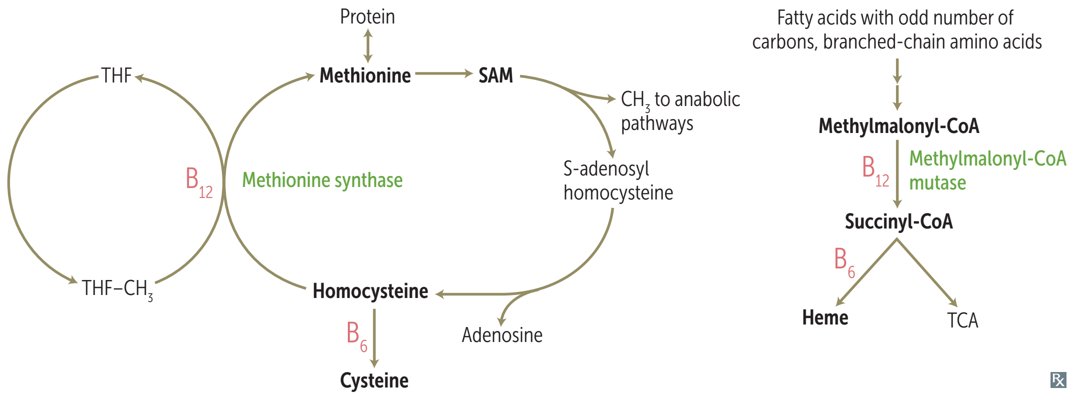
Deficiency can be caused by several drugs (eg, phenytoin, sulfonamides, methotrexate).

Supplemental folic acid at least 1 month prior to conception and during early pregnancy to ↓ risk of neural tube defects. Give vitamin $B_9$ for the **9** months of pregnancy.

## Vitamin $B_{12}$

Also called cobalamin.

| | | |
|---|---|---|
| FUNCTION | Cofactor for methionine synthase (transfers $CH_3$ groups as methylcobalamin) and methylmalonyl-CoA mutase. Important for DNA synthesis. | Found in animal products.<br>Synthesized only by microorganisms. Very large reserve pool (several years) stored primarily in the liver. Deficiency caused by malabsorption (eg, sprue, enteritis, *Diphyllobothrium latum*, achlorhydria, bacterial overgrowth, alcohol overuse), lack of intrinsic factor (eg, pernicious anemia, gastric bypass surgery), absence of terminal ileum (surgical resection, eg, for Crohn disease), certain drugs (eg, metformin), or insufficient intake (eg, veganism).<br>$B_9$ supplementation can mask the hematologic symptoms of $B_{12}$ deficiency, but not the neurologic symptoms. |
| DEFICIENCY | Macrocytic, megaloblastic anemia; hypersegmented PMNs; paresthesias and subacute combined degeneration (degeneration of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts) due to abnormal myelin. Associated with ↑ serum homocysteine and methylmalonic acid levels, along with 2° folate deficiency. Prolonged deficiency → irreversible nerve damage. | |




## Vitamin C

Also called ascorbic acid.

| | | |
|---|---|---|
| FUNCTION | Antioxidant; also facilitates iron absorption by reducing it to $Fe^{2+}$ state. Necessary for hydroxylation of proline and lysine in collagen synthesis. Necessary for dopamine β-hydroxylase (converts dopamine to NE). | Found in fruits and vegetables.<br>Pronounce "**absorb**ic" acid.<br>Ancillary treatment for methemoglobinemia by reducing $Fe^{3+}$ to $Fe^{2+}$. |
| DEFICIENCY | Scurvy—swollen gums, easy bruising, petechiae, hemarthrosis, anemia, poor wound healing, perifollicular and subperiosteal hemorrhages, "corkscrew" hair.<br>Weakened immune response. | Deficiency may be precipitated by tea and toast diet.<br>Vitamin **C** deficiency causes s**C**urvy due to a **C**ollagen hydro**C**ylation defect. |
| EXCESS | Nausea, vomiting, diarrhea, fatigue, calcium oxalate nephrolithiasis. Can ↑ iron toxicity in predisposed individuals by increasing dietary iron absorption (ie, can worsen hemochromatosis or transfusion-related iron overload). | |

## Vitamin D

$D_3$ (cholecalciferol) from exposure of skin (stratum basale) to sun, ingestion of fish, milk, plants.
$D_2$ (ergocalciferol) from ingestion of plants, fungi, yeasts.
Both converted to 25-OH $D_3$ (storage form) in liver and to the active form 1,25-$(OH)_2$ $D_3$ (calcitriol) in kidney.

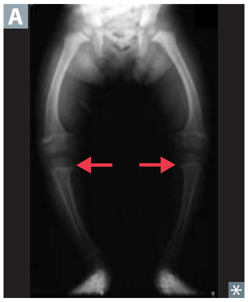
**FUNCTION**

↑ intestinal absorption of $Ca^{2+}$ and $PO_4^{3-}$.
↑ bone mineralization at low levels.
↑ bone resorption at higher levels.

**REGULATION**

↑ PTH, ↓ $Ca^{2+}$, ↓ $PO_4^{3-}$ → ↑ 1,25-$(OH)_2D_3$ production.
1,25-$(OH)_2D_3$ feedback inhibits its own production.
↑ PTH → ↑ $Ca^{2+}$ reabsorption and ↓ $PO_4^{3-}$ reabsorption in the kidney.

**DEFICIENCY**



Rickets in children (deformity, such as genu varum "bowlegs" A), osteomalacia in adults (bone pain and muscle weakness), hypocalcemic tetany.
Caused by malabsorption, ↓ sun exposure, poor diet, chronic kidney disease (CKD), advanced liver disease.
Give oral vitamin D to breastfed infants.
Darker skin and prematurity predispose to deficiency.

**EXCESS**

Hypercalcemia, hypercalciuria, loss of appetite, stupor. Seen in granulomatous diseases (↑ activation of vitamin D by epithelioid macrophages).

## Vitamin E

Includes tocopherol, tocotrienol.

**FUNCTION**

Antioxidant (protects RBCs and membranes from free radical damage).

**DEFICIENCY**

Hemolytic anemia, acanthocytosis, muscle weakness, demyelination of posterior columns (↓ proprioception and vibration sensation) and spinocerebellar tract (ataxia).

Neurologic presentation may appear similar to vitamin $B_{12}$ deficiency, but without megaloblastic anemia, hypersegmented neutrophils, or ↑ serum methylmalonic acid levels.

**EXCESS**

Risk of enterocolitis in infants.

High-dose supplementation may alter metabolism of vitamin K → enhanced anticoagulant effects of warfarin.

## Vitamin K

Includes phytomenadione, phylloquinone, phytonadione, menaquinone.

| | | |
|---|---|---|
| FUNCTION | Activated by epoxide reductase to the reduced form, which is a cofactor for the γ-carboxylation of glutamic acid residues on various proteins required for blood clotting. Synthesized by intestinal flora. | **K** is for **K**oagulation. Necessary for the maturation of clotting factors II, VII, IX, X, and proteins C and S. Warfarin inhibits vitamin K–dependent synthesis of these factors and proteins. |
| DEFICIENCY | Neonatal hemorrhage with ↑ PT and ↑ aPTT but normal bleeding time (neonates have sterile intestines and are unable to synthesize vitamin K). Can also occur after prolonged use of broad-spectrum antibiotics. | Not in breast milk; "breast-fed infants **D**on't **K**now about vitamins **D** and **K**". Neonates are given vitamin K injection at birth to prevent hemorrhagic disease of the newborn. |

## Zinc

FUNCTION

Mineral essential for the activity of 100+ enzymes. Important in the formation of zinc fingers (transcription factor motif).

DEFICIENCY


Delayed wound healing, suppressed immunity, male hypogonadism, ↓ adult hair (axillary, facial, pubic), dysgeusia, anosmia. Associated with acrodermatitis enteropathica (A, defect in intestinal zinc absorption). May predispose to alcoholic cirrhosis.

## Protein-energy malnutrition

### Kwashiorkor

Protein malnutrition resulting in skin lesions, edema due to ↓ plasma oncotic pressure (due to low serum albumin), liver malfunction (fatty change due to ↓ apolipoprotein synthesis and deposition). Clinical picture is small child with swollen abdomen A.

Kwashiorkor results from protein-deficient **MEALS**:
- **M**alnutrition
- **E**dema
- **A**nemia
- **L**iver (fatty)
- **S**kin lesions (eg, hyperkeratosis, dyspigmentation)

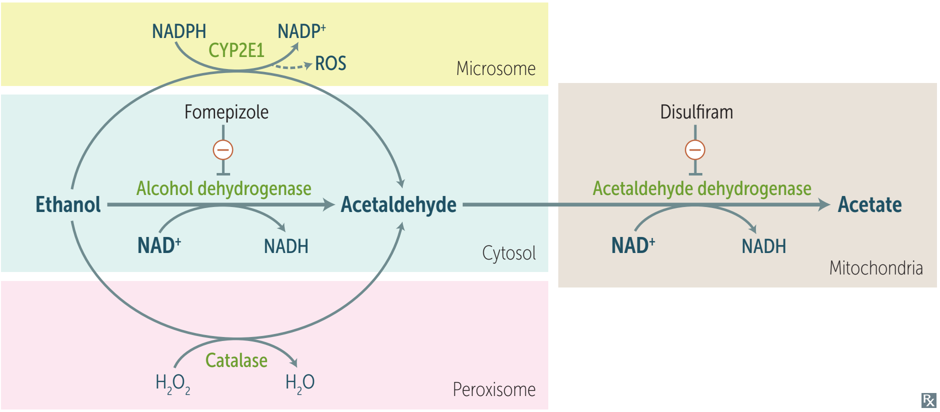


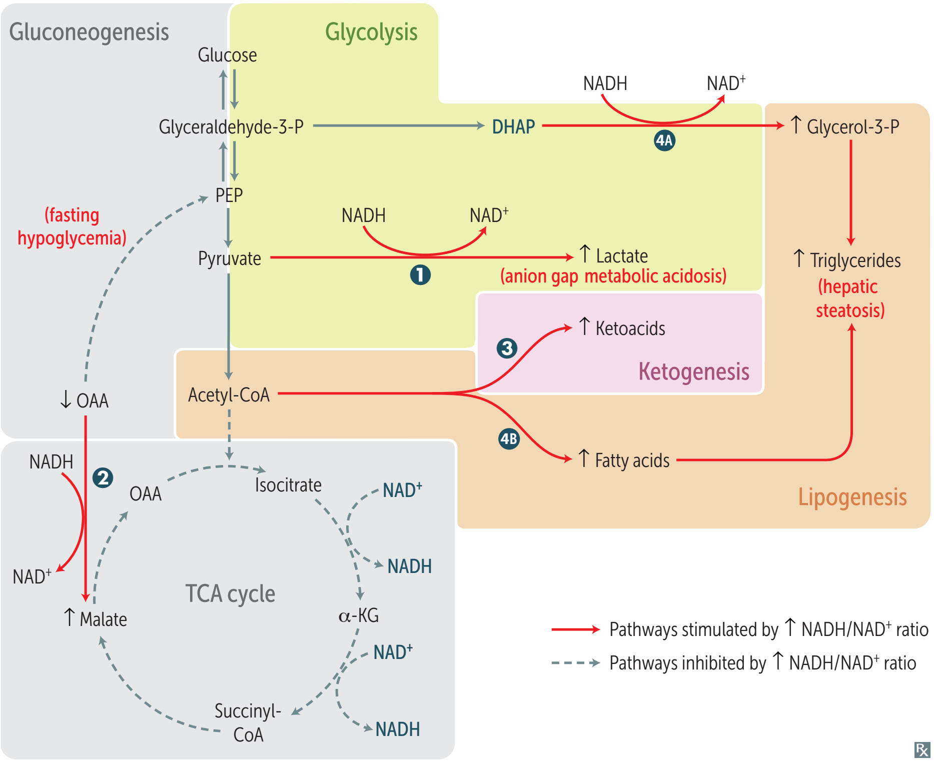
### Marasmus

Malnutrition not causing edema. Diet is deficient in calories but no nutrients are entirely absent.

**M**arasmus results in **m**uscle wasting B.

## Ethanol metabolism




↑ NADH/NAD+ ratio inhibits TCA cycle → ↑ acetyl-CoA used in ketogenesis (→ ketoacidosis), lipogenesis (→ hepatosteatosis).

Females are more susceptible than males to effects of alcohol due to ↓ activity of gastric alcohol dehydrogenase, ↓ body size, ↓ percentage of water in body weight.

NAD+ is the limiting reagent.

Alcohol dehydrogenase operates via zero-order kinetics.

Ethanol metabolism ↑ NADH/NAD+ ratio in liver, causing:

1. Lactic acidosis—↑ pyruvate conversion to lactate
2. Fasting hypoglycemia—↓ gluconeogenesis due to ↑ conversion of OAA to malate
3. Ketoacidosis—diversion of acetyl-CoA into ketogenesis rather than TCA cycle
4. Hepatosteatosis—↑ conversion of DHAP to glycerol-3-P 4A; acetyl-CoA diverges into fatty acid synthesis 4B, which combines with glycerol-3-P to synthesize triglycerides

**Fome**pizole—blocks alcohol dehydrogenase; preferred antidote **for** **o**verdoses of **me**thanol or **e**thylene glycol. Alcohol dehydrogenase has higher affinity for ethanol than for methanol or ethylene glycol → ethanol can be used as competitive inhibitor of alcohol dehydrogenase to treat methanol or ethylene glycol poisoning.

**Dis**ulfiram—blocks acetaldehyde dehydrogenase → ↑ acetaldehyde → ↑ hangover symptoms → **dis**couraging drinking.

## ▸ BIOCHEMISTRY—METABOLISM

| | |
|---|---|
| **Enzyme terminology** | An enzyme's name often describes its function. For example, glucokinase is an enzyme that catalyzes the phosphorylation of glucose using a molecule of ATP. The following are commonly used enzyme descriptors. |
| **Kinase** | Catalyzes transfer of a phosphate group from a high-energy molecule (usually ATP) to a substrate (eg, phosphofructokinase). |
| **Phosphorylase** | Adds inorganic phosphate onto substrate without using ATP (eg, glycogen phosphorylase). |
| **Phosphatase** | Removes phosphate group from substrate (eg, fructose-1,6-bisphosphatase 1). |
| **Dehydrogenase** | Catalyzes oxidation-reduction reactions (eg, pyruvate dehydrogenase). |
| **Hydroxylase** | Adds hydroxyl group (−OH) onto substrate (eg, tyrosine hydroxylase). |
| **Carboxylase** | Transfers $CO_2$ groups with the help of biotin (eg, pyruvate carboxylase). |
| **Mutase** | Relocates a functional group within a molecule (eg, vitamin $B_{12}$–dependent methylmalonyl-CoA mutase). |
| **Synthase/synthetase** | Joins two molecules together using a source of energy (eg, ATP, acetyl-CoA, nucleotide sugar). |

### Rate-determining enzymes of metabolic processes

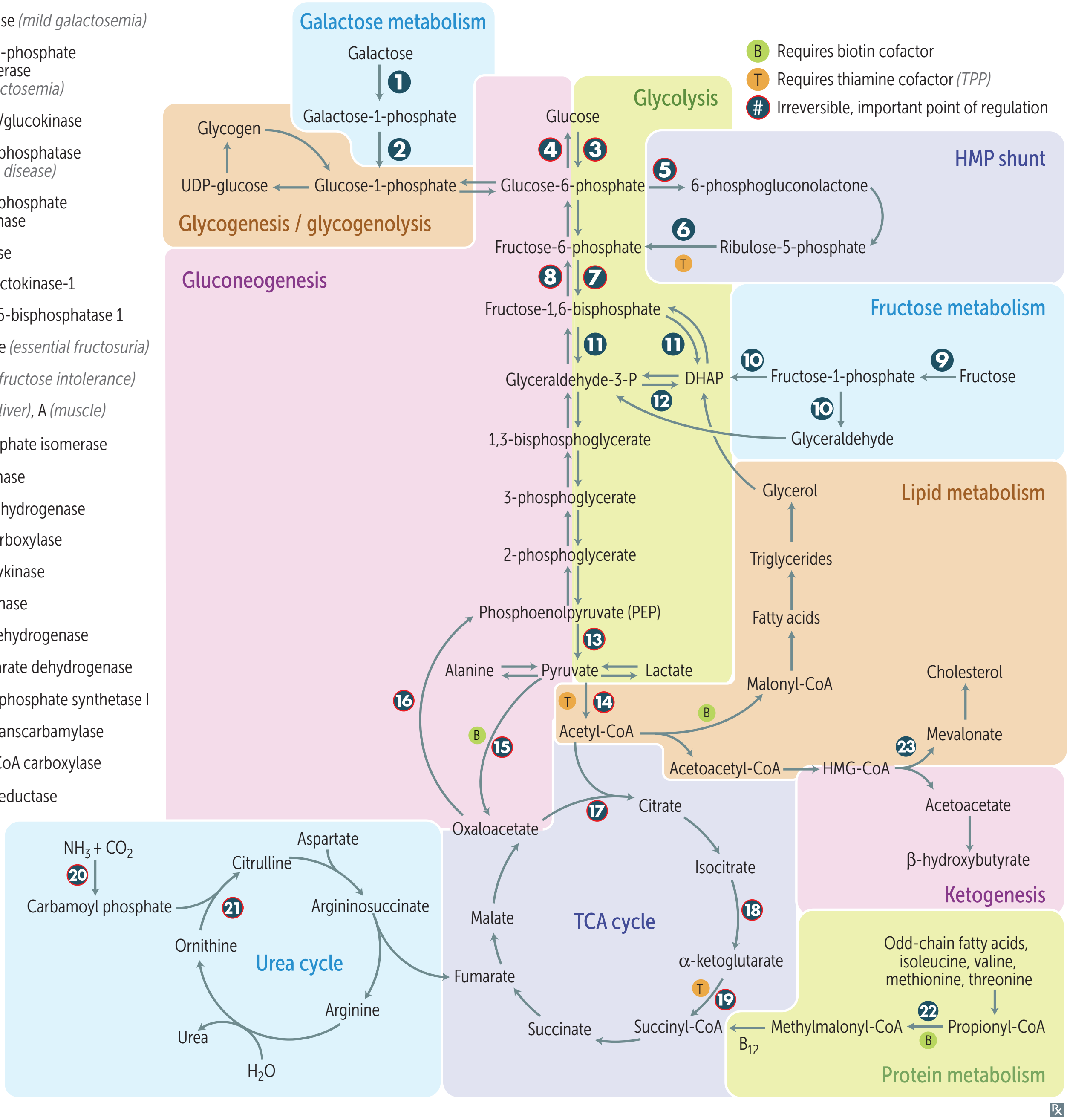
| PROCESS | ENZYME | REGULATORS |
|---|---|---|
| **Glycolysis** | Phosphofructokinase-1 (PFK-1) | AMP ⊕, fructose-2,6-bisphosphate ⊕<br>ATP ⊖, citrate ⊖ |
| **Gluconeogenesis** | Fructose-1,6-bisphosphatase 1 | AMP ⊖, fructose-2,6-bisphosphate ⊖ |
| **TCA cycle** | Isocitrate dehydrogenase | ADP ⊕<br>ATP ⊖, NADH ⊖ |
| **Glycogenesis** | Glycogen synthase | Glucose-6-phosphate ⊕, insulin ⊕, cortisol ⊕<br>Epinephrine ⊖, glucagon ⊖ |
| **Glycogenolysis** | Glycogen phosphorylase | Epinephrine ⊕, glucagon ⊕, AMP ⊕<br>Glucose-6-phosphate ⊖, insulin ⊖, ATP ⊖ |
| **HMP shunt** | Glucose-6-phosphate dehydrogenase (G6PD) | $NADP^+$ ⊕<br>NADPH ⊖ |
| **De novo pyrimidine synthesis** | Carbamoyl phosphate synthetase II | ATP ⊕, PRPP ⊕<br>UTP ⊖ |
| **De novo purine synthesis** | Glutamine-phosphoribosylpyrophosphate (PRPP) amidotransferase | AMP ⊖, inosine monophosphate (IMP) ⊖, GMP ⊖ |
| **Urea cycle** | Carbamoyl phosphate synthetase I | N-acetylglutamate ⊕ |
| **Fatty acid synthesis** | Acetyl-CoA carboxylase (ACC) | Insulin ⊕, citrate ⊕<br>Glucagon ⊖, palmitoyl-CoA ⊖ |
| **Fatty acid oxidation** | Carnitine acyltransferase I | Malonyl-CoA ⊖ |
| **Ketogenesis** | HMG-CoA synthase | |
| **Cholesterol synthesis** | HMG-CoA reductase | Insulin ⊕, thyroxine ⊕, estrogen ⊕<br>Glucagon ⊖, cholesterol ⊖ |

## Metabolism sites

| | |
|---|---|
| **Mitochondria** | Fatty acid oxidation (β-oxidation), acetyl-CoA production, TCA cycle, oxidative phosphorylation, ketogenesis. |
| **Cytoplasm** | Glycolysis, HMP shunt, and synthesis of cholesterol (SER), proteins (ribosomes, RER), fatty acids, and nucleotides. |
| **Both** | Heme synthesis, urea cycle, gluconeogenesis. Hugs take two (both). |

## Summary of pathways

1. Galactokinase *(mild galactosemia)*
2. Galactose-1-phosphate uridyltransferase *(severe galactosemia)*
3. Hexokinase/glucokinase
4. Glucose-6-phosphatase *(von Gierke disease)*
5. Glucose-6-phosphate dehydrogenase
6. Transketolase
7. Phosphofructokinase-1
8. Fructose-1,6-bisphosphatase 1
9. Fructokinase *(essential fructosuria)*
10. Aldolase B *(fructose intolerance)*
11. Aldolase B *(liver)*, A *(muscle)*
12. Triose phosphate isomerase
13. Pyruvate kinase
14. Pyruvate dehydrogenase
15. Pyruvate carboxylase
16. PEP carboxykinase
17. Citrate synthase
18. Isocitrate dehydrogenase
19. α-ketoglutarate dehydrogenase
20. Carbamoyl phosphate synthetase I
21. Ornithine transcarbamylase
22. Propionyl-CoA carboxylase
23. HMG-CoA reductase



**ATP production**

Aerobic metabolism of one glucose molecule produces 32 net ATP via malate-aspartate shuttle (heart and liver), 30 net ATP via glycerol-3-phosphate shuttle (muscle).
Anaerobic glycolysis produces only 2 net ATP per glucose molecule.
ATP hydrolysis can be coupled to energetically unfavorable reactions.

Arsenic causes glycolysis to produce zero net ATP.

**Activated carriers**

| CARRIER MOLECULE | CARRIED IN ACTIVATED FORM |
|---|---|
| ATP | Phosphoryl groups |
| NADH, NADPH, $FADH_2$ | Electrons |
| CoA, lipoamide | Acyl groups |
| Biotin | $CO_2$ |
| Tetrahydrofolates | 1-carbon units |
| S-adenosylmethionine (SAM) | $CH_3$ groups |
| TPP | Aldehydes |

**Universal electron acceptors**

Nicotinamides ($NAD^+$, $NADP^+$ from vitamin $B_3$) and flavin nucleotides (FAD from vitamin $B_2$).
$NAD^+$ is generally used in **catabolic** processes to carry reducing equivalents away as NADH.
NADPH is used in **anabolic** processes (eg, steroid and fatty acid synthesis) as a supply of reducing equivalents.

NADPH is a product of the HMP shunt.
NADPH is used in:
- Anabolic processes
- Respiratory burst
- Cytochrome P-450 system
- Glutathione reductase

**Hexokinase vs glucokinase**

Phosphorylation of glucose to yield glucose-6-phosphate is catalyzed by glucokinase in the liver and hexokinase in other tissues. Hexokinase sequesters glucose in tissues, where it is used even when glucose concentrations are low. At high glucose concentrations, glucokinase helps to store glucose in liver. Glucokinase deficiency is a cause of maturity onset diabetes of the young (MODY) and gestational diabetes.

| | Hexokinase | Glucokinase |
|---|---|---|
| Location | Most tissues, except liver and pancreatic β cells | Liver, β cells of pancreas |
| $K_m$ | Lower (↑ affinity) | Higher (↓ affinity) |
| $V_{max}$ | Lower (↓ capacity) | Higher (↑ capacity) |
| Induced by insulin | No | Yes |
| Feedback inhibition by | Glucose-6-phosphate | Fructose-6-phosphate |

## Glycolysis regulation, key enzymes

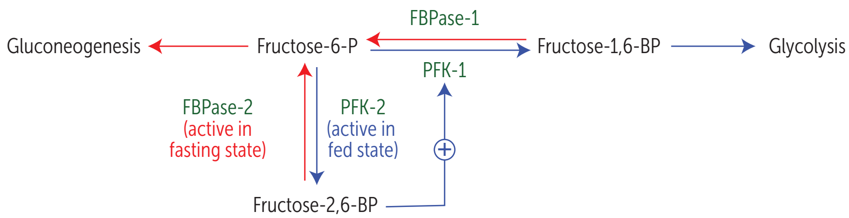
Net glycolysis (cytoplasm):
Glucose + 2 $P_i$ + 2 ADP + 2 $NAD^+$ → 2 pyruvate + 2 ATP + 2 NADH + 2 $H^+$ + 2 $H_2O$.

Equation not balanced chemically, and exact balanced equation depends on ionization state of reactants and products.

| | | |
|---|---|---|
| REQUIRE ATP | Glucose $\xrightarrow{\text{Hexokinase/glucokinase}}$ Glucose-6-P | Glucose-6-P ⊖ hexokinase.<br>Fructose-6-P ⊖ glucokinase. |
| | Fructose-6-P $\xrightarrow{\text{Phosphofructokinase-1}}$ Fructose-1,6-BP<br>(rate-limiting step) | AMP ⊕, fructose-2,6-bisphosphate ⊕.<br>ATP ⊖, citrate ⊖. |
| PRODUCE ATP | 1,3-BPG $\xleftrightarrow{\text{Phosphoglycerate kinase}}$ 3-PG | |
| | Phosphoenolpyruvate $\xrightarrow{\text{Pyruvate kinase}}$ Pyruvate | Fructose-1,6-bisphosphate ⊕.<br>ATP ⊖, alanine ⊖, glucagon ⊖. |

## Regulation by fructose-2,6-bisphosphate

Fructose bisphosphatase-2 (FBPase-2) and phosphofructokinase-2 (PFK-2) are the same bifunctional enzyme whose function is reversed by phosphorylation by protein kinase A.




Fasting state: ↑ glucagon → ↑ cAMP → ↑ protein kinase A → ↑ FBPase-2, ↓ PFK-2, less glycolysis, more gluconeogenesis.

**F**a**B**ian the **P**easant **(FBP)** has to work hard when starving.

Fed state: ↑ insulin → ↓ cAMP → ↓ protein kinase A → ↓ FBPase-2, ↑ PFK-2, more glycolysis, less gluconeogenesis.

**P**rince **F**rederic**K** **(PFK)** works only when fed.

## Pyruvate dehydrogenase complex

Mitochondrial enzyme complex linking glycolysis and TCA cycle. Differentially regulated in fed (active)/fasting (inactive) states.
Reaction: pyruvate + $NAD^+$ + CoA → acetyl-CoA + $CO_2$ + NADH.
Contains 3 enzymes requiring 5 cofactors:

1. **T**hiamine pyrophosphate ($B_1$)
2. **L**ipoic acid
3. **C**oA ($B_5$, pantothenic acid)
4. **F**AD ($B_2$, riboflavin)
5. **N**$AD^+$ ($B_3$, niacin)

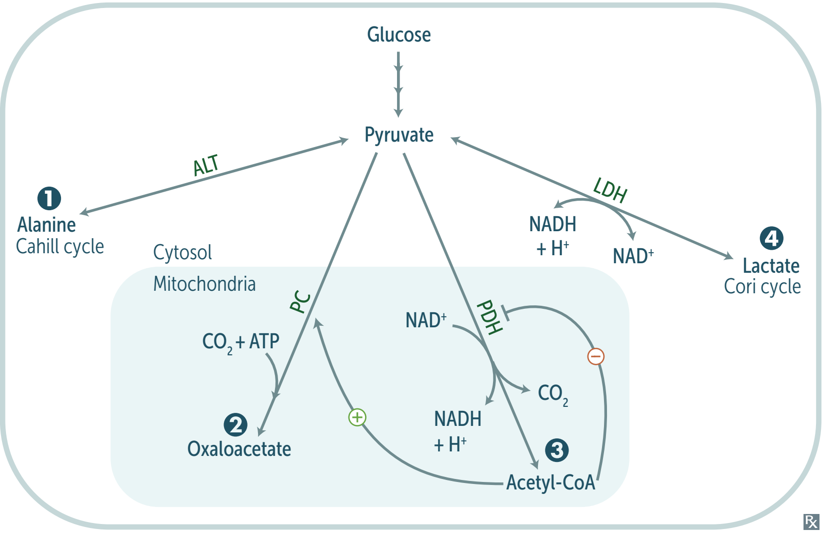
Activated by: ↑ $NAD^+$/NADH ratio, ↑ ADP ↑ $Ca^{2+}$.

The complex is similar to the α-ketoglutarate dehydrogenase complex (same cofactors, similar substrate and action), which converts α-ketoglutarate → succinyl-CoA (TCA cycle).

**T**he **l**ovely **c**oenzymes **f**or **n**erds.
Arsenic inhibits lipoic acid. Arsenic poisoning clinical findings: imagine a vampire (pigmentary skin changes, skin cancer), vomiting and having diarrhea, running away from a cutie (QT prolongation) with garlic breath.

| | |
|---|---|
| **Pyruvate dehydrogenase complex deficiency** | Causes a buildup of pyruvate that gets shunted to lactate (via LDH) and alanine (via ALT). X-linked. |
| FINDINGS | Neurologic defects, lactic acidosis, ↑ serum alanine starting in infancy. |
| TREATMENT | ↑ intake of ketogenic nutrients (eg, high fat content or ↑ lysine and leucine). |

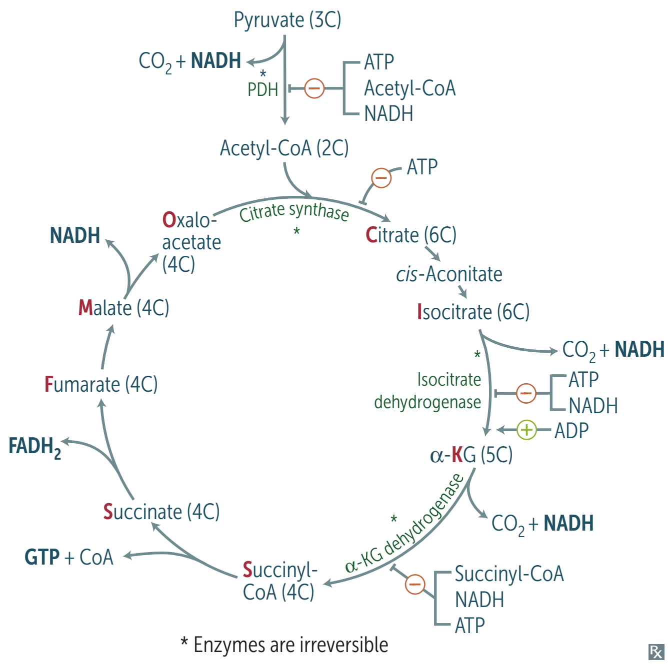
## Pyruvate metabolism




Functions of different pyruvate metabolic pathways (and their associated cofactors):

1. Alanine aminotransferase ($B_6$): alanine carries amino groups to the liver from muscle
2. Pyruvate carboxylase ($B_7$): oxaloacetate can replenish TCA cycle or be used in gluconeogenesis
3. Pyruvate dehydrogenase ($B_1$, $B_2$, $B_3$, $B_5$, lipoic acid): transition from glycolysis to the TCA cycle
4. Lactic acid dehydrogenase ($B_3$): end of anaerobic glycolysis (major pathway in RBCs, WBCs, kidney medulla, lens, testes, and cornea)

## TCA cycle




Also called Krebs cycle. Pyruvate → acetyl-CoA produces 1 NADH, 1 $CO_2$.

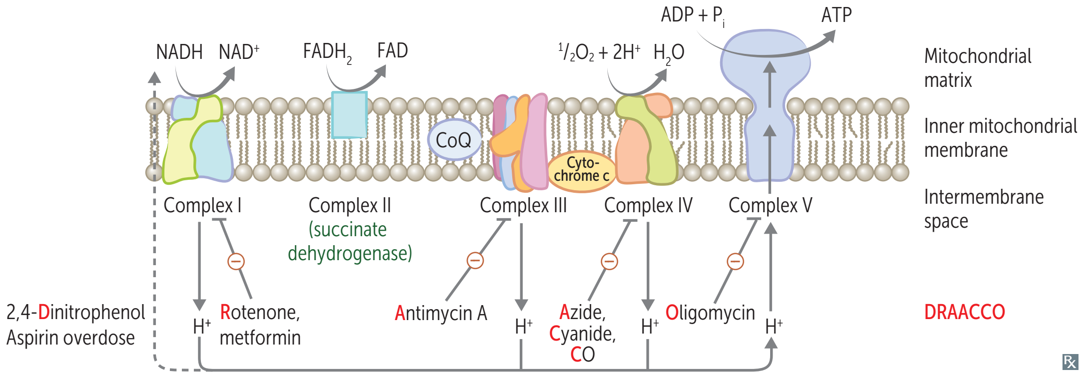
The TCA cycle produces 3 NADH, 1 $FADH_2$, 2 $CO_2$, 1 GTP per acetyl-CoA = 10 ATP/acetyl-CoA (2× everything per glucose). TCA cycle reactions occur in the mitochondria.

α-ketoglutarate dehydrogenase complex requires the same cofactors as the pyruvate dehydrogenase complex (vitamins $B_1$, $B_2$, $B_3$, $B_5$, lipoic acid).

**C**itrate **i**s **K**rebs' **s**tarting **s**ubstrate **f**or **m**aking **o**xaloacetate.

## Electron transport chain and oxidative phosphorylation

NADH electrons from glycolysis enter mitochondria via the malate-aspartate or glycerol-3-phosphate shuttle. $FADH_2$ electrons are transferred to complex II (at a lower energy level than NADH). The passage of electrons results in the formation of a proton gradient that, coupled to oxidative phosphorylation, drives the production of ATP.




| ATP PRODUCED VIA ATP SYNTHASE | | |
|---|---|---|
| | 1 NADH → 2.5 ATP; 1 $FADH_2$ → 1.5 ATP. | |
| **OXIDATIVE PHOSPHORYLATION POISONS** | | |
| **Electron transport inhibitors** | Directly inhibit electron transport, causing a ↓ proton gradient and block of ATP synthesis. | Rotenone: complex one inhibitor.<br>"An-3-mycin" (antimycin) A: complex 3 inhibitor.<br>Cyanide, carbon monoxide, azide (the -ides, 4 letters) inhibit complex IV. |
| **ATP synthase inhibitors** | Directly inhibit mitochondrial ATP synthase, causing an ↑ proton gradient. No ATP is produced because electron transport stops. | Oligomycin. |
| **Uncoupling agents** | ↑ permeability of membrane, causing a ↓ proton gradient and ↑ $O_2$ consumption. ATP synthesis stops, but electron transport continues. Produces heat. | 2,4-Dinitrophenol (used illicitly for weight loss), aspirin (fevers often occur after overdose), thermogenin in brown fat (has more mitochondria than white fat). |

## Gluconeogenesis, irreversible enzymes

| | | Pathway produces fresh glucose. |
|---|---|---|
| **Pyruvate carboxylase** | In mitochondria. Pyruvate → oxaloacetate. | Requires biotin, ATP. Activated by acetyl-CoA. |
| **Phosphoenolpyruvate carboxykinase** | In cytosol. Oxaloacetate → phosphoenolpyruvate (PEP). | Requires GTP. |
| **Fructose-1,6-bisphosphatase 1** | In cytosol. Fructose-1,6-bisphosphate → fructose-6-phosphate. | Citrate ⊕, AMP ⊖, fructose 2,6-bisphosphate ⊖. |
| **Glucose-6-phosphatase** | In ER. Glucose-6-phosphate → glucose. | |

Occurs primarily in liver; serves to maintain euglycemia during fasting. Enzymes also found in kidney, intestinal epithelium. Deficiency of the key gluconeogenic enzymes causes hypoglycemia. (Muscle cannot participate in gluconeogenesis because it lacks glucose-6-phosphatase).

Odd-chain fatty acids yield 1 propionyl-CoA during metabolism, which can enter the TCA cycle (as succinyl-CoA), undergo gluconeogenesis, and serve as a glucose source (It's odd for fatty acids to make glucose). Even-chain fatty acids cannot produce new glucose, since they yield only acetyl-CoA equivalents.

**Pentose phosphate pathway**

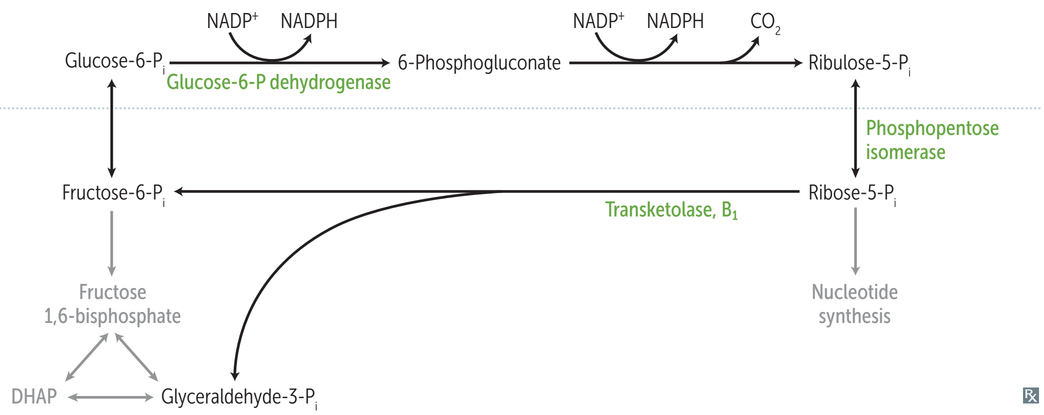
Also called HMP shunt. Provides a source of NADPH from abundantly available glucose-6-P (NADPH is required for reductive reactions, eg, glutathione reduction inside RBCs, fatty acid and cholesterol biosynthesis). Additionally, this pathway yields ribose for nucleotide synthesis. Two distinct phases (oxidative and nonoxidative), both of which occur in the cytoplasm. No ATP is used or produced.

Sites: lactating mammary glands, liver, adrenal cortex (sites of fatty acid or steroid synthesis), RBCs.

REACTIONS

**Oxidative (irreversible)**

**Nonoxidative (reversible)**



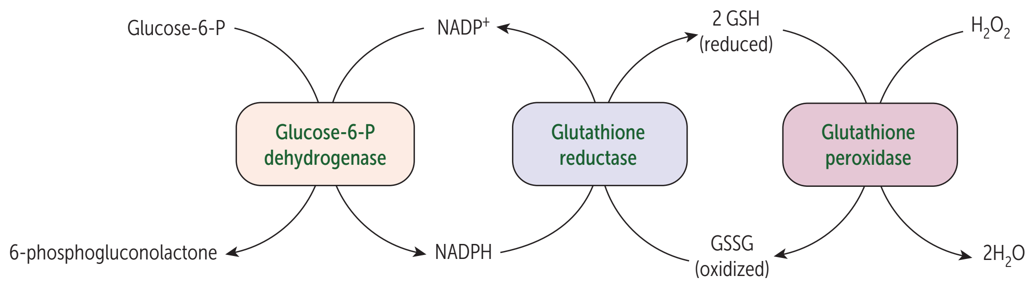

**Glucose-6-phosphate dehydrogenase deficiency**

NADPH is necessary to keep glutathione reduced, which in turn detoxifies free radicals and peroxides. ↓ NADPH in RBCs leads to hemolytic anemia due to poor RBC defense against oxidizing agents (eg, fava beans, sulfonamides, nitrofurantoin, primaquine/chloroquine, antituberculosis drugs). Infection (most common cause) can also precipitate hemolysis; inflammatory response produces free radicals that diffuse into RBCs, causing oxidative damage.

X-linked recessive disorder; most common human enzyme deficiency; more prevalent among descendants of populations in malaria-endemic regions (eg, sub-Saharan Africa, Southeast Asia).

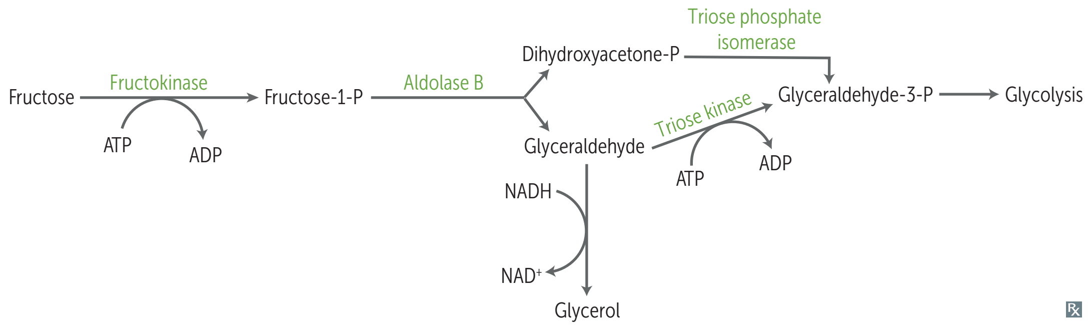
Heinz bodies—denatured globin chains precipitate within RBCs due to oxidative stress.

**Bite cells**—result from the phagocytic removal of **Heinz** bodies by splenic macrophages. Think, "**Bite** into some **Heinz** ketchup."



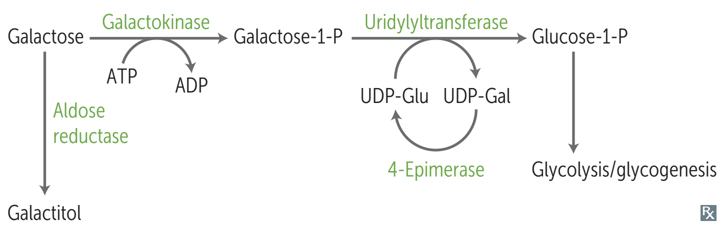
## Disorders of fructose metabolism

| | |
|---|---|
| **Essential fructosuria** | Involves a defect in **fructokinase**. Autosomal recessive. A benign, asymptomatic condition (fructo**kin**ase deficiency is **kin**der), since fructose is not trapped in cells. Hexokinase becomes 1° pathway for converting fructose to fructose-6-phosphate.<br>Symptoms: fructose appears in blood and urine.<br>Disorders of fructose metabolism cause milder symptoms than analogous disorders of galactose metabolism. |
| **Hereditary fructose intolerance** | Hereditary deficiency of **aldolase B**. Autosomal recessive. Fructose-1-phosphate accumulates, causing a ↓ in available phosphate, which results in inhibition of glycogenolysis and gluconeogenesis. Symptoms present following consumption of fruit, juice, or honey. Urine dipstick will be ⊖ (tests for glucose only); reducing sugar can be detected in the urine (nonspecific test for inborn errors of carbohydrate metabolism).<br>Symptoms: hypoglycemia, jaundice, cirrhosis, vomiting.<br>Treatment: ↓ intake of fructose, sucrose (glucose + fructose), and sorbitol (metabolized to fructose). |




## Disorders of galactose metabolism

| | |
|---|---|
| **Galactokinase deficiency** | Hereditary deficiency of **galactokinase**. Galactitol accumulates if galactose is present in diet. Relatively mild condition. Autosomal recessive.<br>Symptoms: galactose appears in blood (galactosemia) and urine (galactosuria); infantile cataracts. May present as failure to track objects or to develop a social smile. Galacto**kin**ase deficiency is **kin**der (benign condition). |
| **Classic galactosemia** | Absence of **galactose-1-phosphate uridyltransferase**. Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol, which accumulates in the lens of the eye).<br>Symptoms develop when infant begins feeding (lactose present in breast milk and routine formula) and include failure to thrive, jaundice, hepatomegaly, infantile cataracts, intellectual disability. Can predispose to *E coli* sepsis in neonates.<br>Treatment: exclude galactose and lactose (galactose + glucose) from diet. |




**F**ructose is to **A**ldolase **B** as **G**alactose is to **U**ridyl**T**ransferase (**FAB GUT**).
The more serious defects lead to $PO_4^{3-}$ depletion.

## Sorbitol

An alternative method of trapping glucose in the cell is to convert it to its alcohol counterpart, sorbitol, via aldose reductase. Some tissues then convert sorbitol to fructose using sorbitol dehydrogenase; tissues with an insufficient amount/activity of this enzyme are at risk of intracellular sorbitol accumulation, causing osmotic damage (eg, cataracts, retinopathy, and peripheral neuropathy seen with chronic hyperglycemia in diabetes).

High blood levels of galactose also result in conversion to the osmotically active galactitol via aldose reductase.

**L**iver, **o**varies, and **se**minal vesicles have both enzymes (they **lose** sorbitol).

$$\text{Glucose} \xrightarrow[\text{NADPH}]{\text{Aldose reductase}} \text{Sorbitol} \xrightarrow[\text{NAD}^+]{\text{Sorbitol dehydrogenase}} \text{Fructose}$$

**L**ens has primarily **A**ldose reductase. **R**etina, **K**idneys, and **S**chwann cells have only aldose reductase (**LARKS**).

## Lactase deficiency

Insufficient lactase enzyme → dietary lactose intolerance. Lactase functions on the intestinal brush border to digest lactose (in milk and milk products) into glucose and galactose.

Primary: age-dependent decline after childhood (absence of lactase-persistent allele), common in people of Asian, African, or Native American descent.

Secondary: loss of intestinal brush border due to gastroenteritis (eg, rotavirus), autoimmune disease.

Congenital lactase deficiency: rare, due to defective gene.

Stool demonstrates ↓ pH and breath shows ↑ hydrogen content with lactose hydrogen breath test ($H^+$ is produced when colonic bacteria ferment undigested lactose). Intestinal biopsy reveals normal mucosa in patients with hereditary lactose intolerance.

### FINDINGS

Bloating, cramps, flatulence, osmotic diarrhea.

### TREATMENT

Avoid dairy products or add lactase pills to diet; lactose-free milk.

## Amino acids

Only L-amino acids are found in proteins.

### Essential

**PVT TIM HaLL**: **P**henylalanine, **V**aline, **T**ryptophan, **T**hreonine, **I**soleucine, **M**ethionine, **H**istidine, **L**eucine, **L**ysine.

Glucogenic: **Met**hionine, **his**tidine, **val**ine. We **met his val**entine, who is so **sweet** (**gluco**genic).

Glucogenic/ketogenic: Isoleucine, phenylalanine, threonine, tryptophan.

Ketogenic: **l**eucine, **l**ysine. The on**l**y pure**l**y ketogenic amino acids.

### Acidic

Aspartic **acid**, glutamic **acid**.

Negatively charged at body pH.

### Basic

**Ar**ginine, **his**tidine, **lys**ine.

Arginine is most **basic**. Histidine has no charge at body pH.

Arginine and histidine are required during periods of growth.

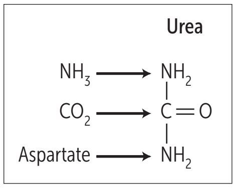
Arginine and lysine are ↑ in histones which bind negatively charged DNA.

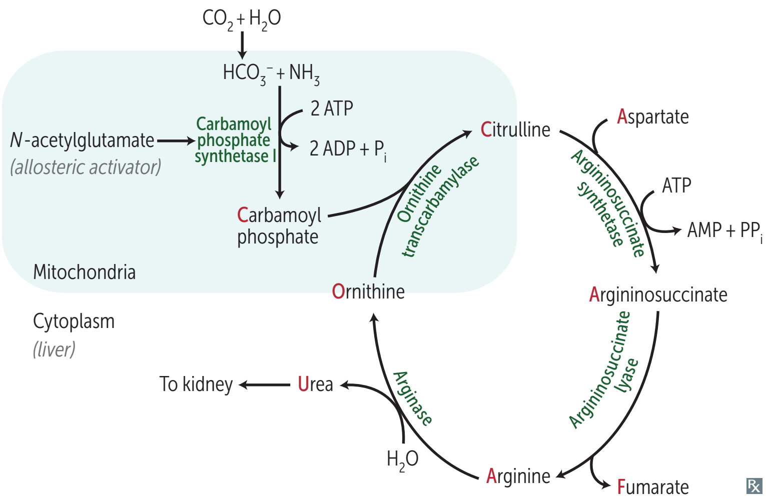
**His lys** (lies) **are basic**.

## Urea cycle

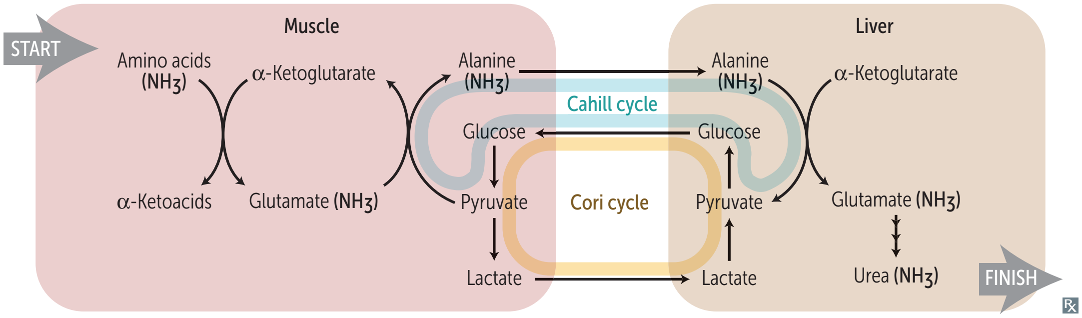
Amino acid catabolism generates common metabolites (eg, pyruvate, acetyl-CoA), which serve as metabolic fuels. Excess nitrogen is converted to urea and excreted by the kidneys.

Ordinarily, Careless Crappers Are Also Frivolous About Urination.




## Transport of ammonia by alanine




## Hyperammonemia

Asterixis

Can be acquired (eg, liver disease) or hereditary (eg, urea cycle enzyme deficiencies).

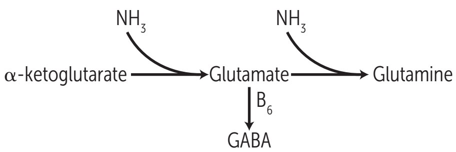
Presents with flapping tremor (asterixis), slurring of speech, somnolence, vomiting, cerebral edema, blurring of vision.

↑ $NH_3$ changes relative amounts of α-ketoglutarate, glutamate, GABA, and glutamine to favor ↑ glutamine. CNS toxicity may involve ↓ GABA, ↓ α-ketoglutarate, TCA cycle inhibition, and cerebral edema due to glutamine-induced osmotic shifts.

Treatment: limit protein in diet.

May be given to ↓ ammonia levels:

- Lactulose to acidify GI tract and trap $NH_4^+$ for excretion.
- Antibiotics (eg, rifaximin, neomycin) to ↓ ammoniagenic bacteria.
- Benzoate, phenylacetate, or phenylbutyrate react with glycine or glutamine, forming products that are excreted renally.

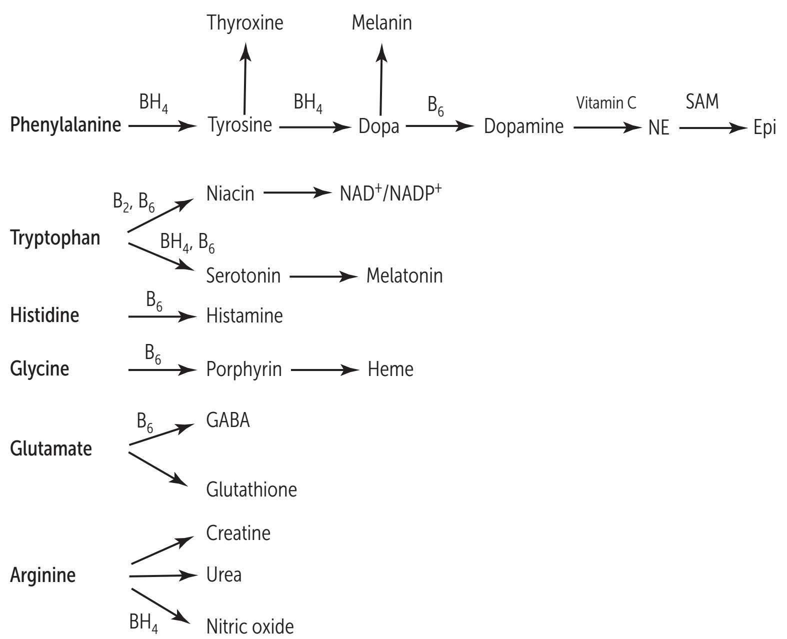


**Ornithine transcarbamylase deficiency**

Most common urea cycle disorder. X-linked recessive (vs other urea cycle enzyme deficiencies, which are autosomal recessive). Interferes with the body's ability to eliminate ammonia. Often evident in the first few days of life, but may present later. Excess carbamoyl phosphate is converted to orotic acid (part of the pyrimidine synthesis pathway).

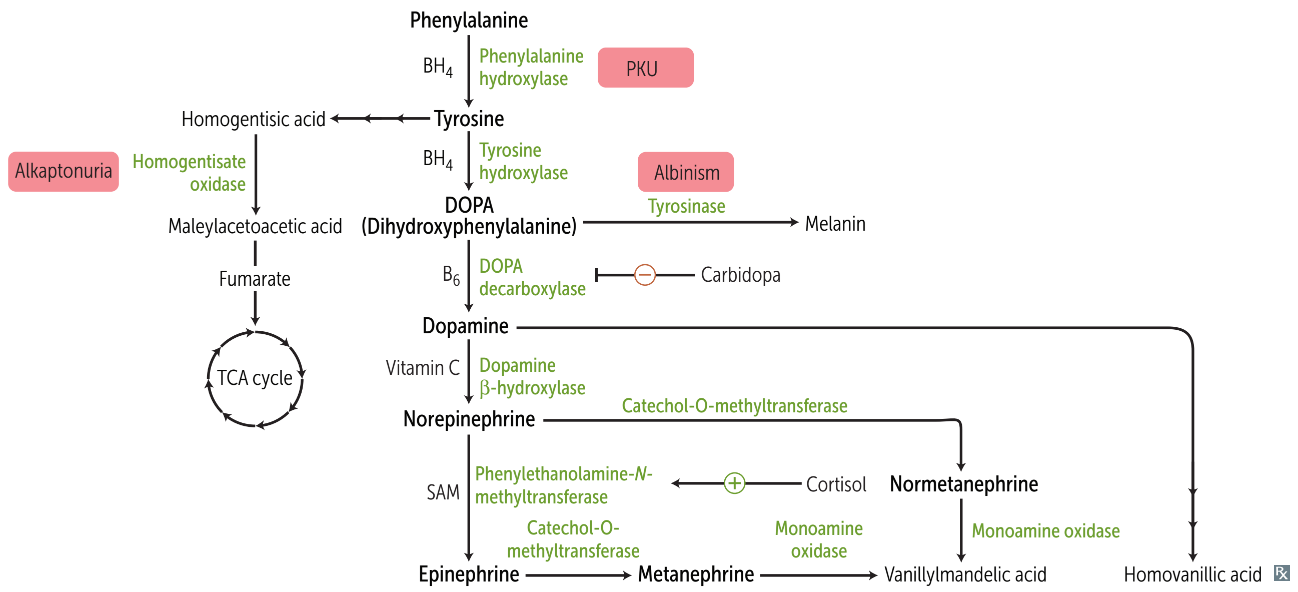
Findings: ↑ orotic acid in blood and urine, ↓ BUN, symptoms of hyperammonemia. No megaloblastic anemia (vs orotic aciduria).

**Amino acid derivatives**




$BH_4$ = tetrahydrobiopterin

**Catecholamine synthesis/tyrosine catabolism**



## Phenylketonuria

Caused by ↓ phenylalanine hydroxylase or ↓ tetrahydrobiopterin ($BH_4$) cofactor (malignant PKU). Tyrosine becomes essential. ↑ phenylalanine → ↑ phenyl ketones in urine.

Findings: intellectual disability, microcephaly, seizures, hypopigmented skin, eczema, musty body odor.

Treatment: ↓ phenylalanine and ↑ tyrosine in diet, tetrahydrobiopterin supplementation.

**Maternal PKU**—due to elevated maternal phenylalanine levels. Can be prevented by dietary intake. Findings in infant: microcephaly, intellectual disability, growth restriction, congenital heart defects.

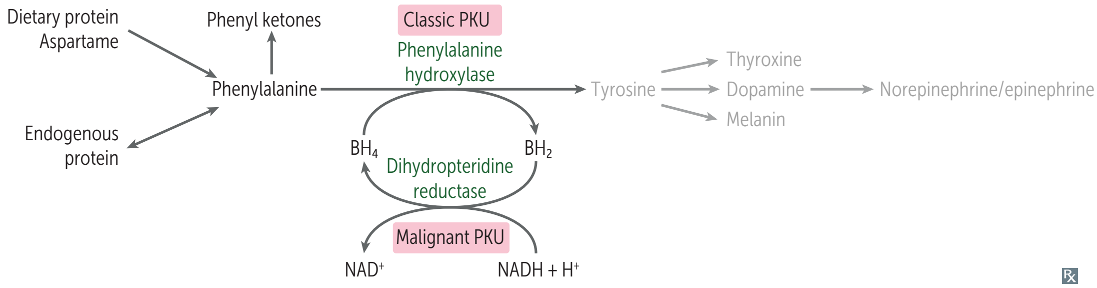
Autosomal recessive. Incidence ≈ 1:10,000.

Screening occurs 2–3 days after birth (normal at birth because of maternal enzyme during fetal life).

Phenyl ketones—phenylacetate, phenyllactate, and phenylpyruvate.

Disorder of **aromatic** amino acid metabolism → musty body **odor**.

PKU patients must avoid the artificial sweetener aspartame, which contains phenylalanine.




## Maple syrup urine disease

Blocked degradation of **branched** amino acids (**I**soleucine, **l**eucine, **v**aline) due to ↓ branched-chain α-ketoacid dehydrogenase ($B_1$). Causes ↑ α-ketoacids in the blood, especially those of leucine.

Treatment: restriction of isoleucine, leucine, valine in diet, and thiamine supplementation.

Autosomal recessive.

Presentation: vomiting, poor feeding, urine smells like maple syrup/burnt sugar. Causes progressive neurological decline.

**I l**ove **V**ermont **maple syrup** from maple trees (with **$B_1$ranches**).

## Alkaptonuria

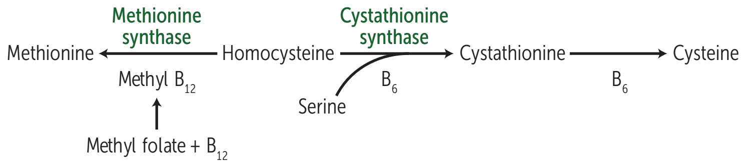

Congenital deficiency of homogentisate oxidase in the degradative pathway of tyrosine to fumarate → pigment-forming homogentisic acid builds up in tissue A. Autosomal recessive. Usually benign.

Findings: bluish-black connective tissue, ear cartilage, and sclerae (ochronosis); urine turns black on prolonged exposure to air. May have debilitating arthralgias (homogentisic acid toxic to cartilage).

### Homocystinuria

Causes (all autosomal recessive):
- Cystathionine synthase deficiency (treatment: ↓ methionine, ↑ cysteine, ↑ $B_6$, $B_{12}$, and folate in diet)
- ↓ affinity of cystathionine synthase for pyridoxal phosphate (treatment: ↑↑ $B_6$ and ↑ cysteine in diet)
- Methionine synthase (homocysteine methyltransferase) deficiency (treatment: ↑ methionine in diet)
- Methylenetetrahydrofolate reductase (MTHFR) deficiency (treatment: ↑ folate in diet)

All forms result in excess homocysteine.
**HOMOCY**stinuria: ↑↑ **H**omocysteine in urine, **O**steoporosis, **M**arfanoid habitus, **O**cular changes (downward and inward lens subluxation), **C**ardiovascular effects (thrombosis and atherosclerosis → stroke and MI), k**Y**phosis, intellectual disability, hypopigmented skin. In homocystinuria, lens subluxes "down and in" (vs Mar**fan**, "up and **fan**s out").




### Cystinuria


Hereditary defect of renal PCT and intestinal amino acid transporter that prevents reabsorption of **C**ystine, **O**rnithine, **L**ysine, and **A**rginine (**COLA**).
Cystine is made of 2 cysteines connected by a disulfide bond.
Excess cystine in the urine can lead to recurrent precipitation of hexagonal cystine stones A.
Treatment: urinary alkalinization (eg, potassium citrate, acetazolamide) and chelating agents (eg, penicillamine) ↑ solubility of cystine stones; good hydration; diet low in methionine.

Autosomal recessive. Common (1:7000).
Cystinuria detected with urinary sodium-cyanide nitroprusside test and proton nuclear magnetic resonance spectroscopy of urine.

### Organic acidemias

Most commonly present in infancy with poor feeding, vomiting, hypotonia, high anion gap metabolic acidosis, hepatomegaly, seizures. Organic acid accumulation:
- Inhibits gluconeogenesis → ↓ fasting blood glucose levels, ↑ ketoacidosis → high anion gap metabolic acidosis
- Inhibits urea cycle → hyperammonemia

#### Propionic acidemia

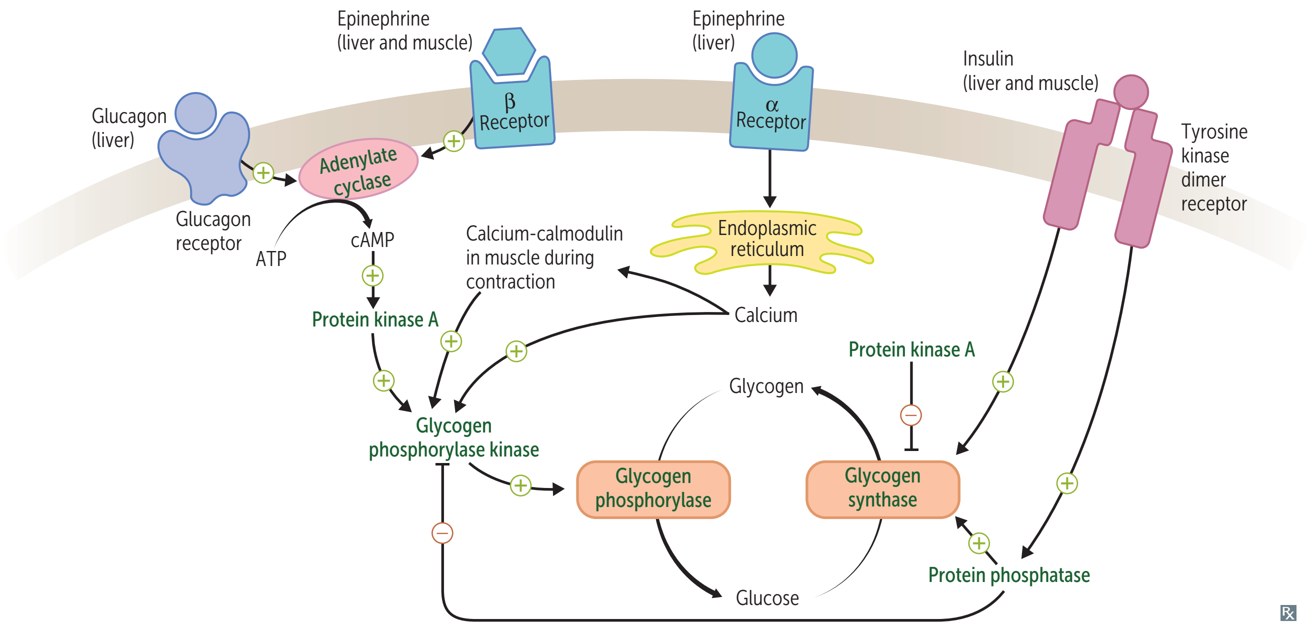
Deficiency of propionyl-CoA carboxylase → ↑ propionyl-CoA, ↓ methylmalonic acid.

#### Methylmalonic acidemia

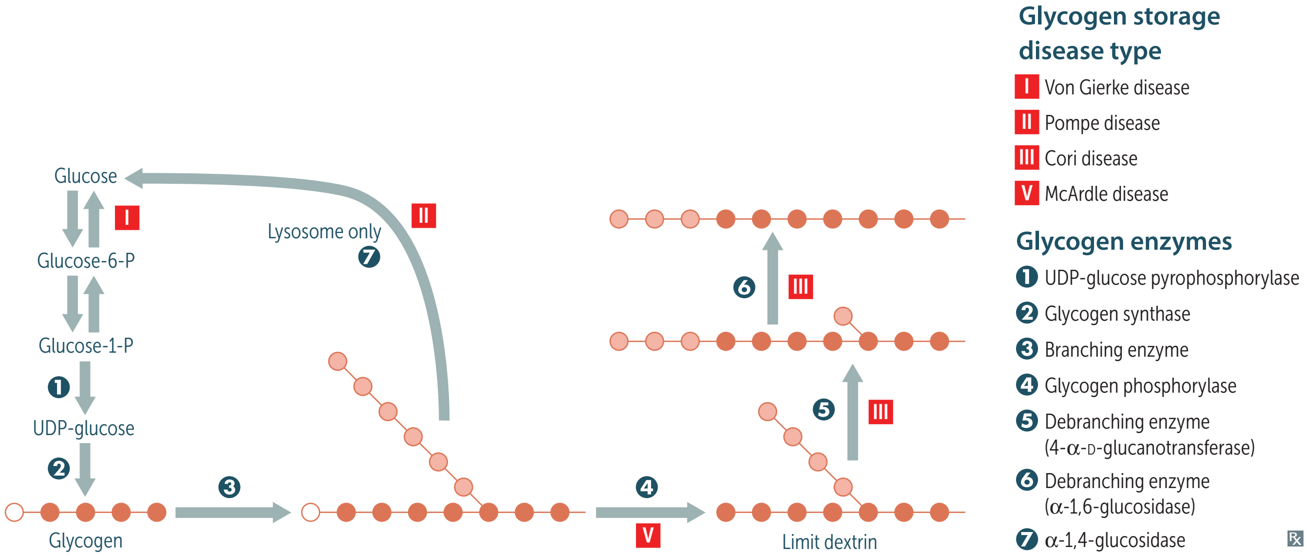
Deficiency of methylmalonyl-CoA mutase or vitamin $B_{12}$.

Treatment (propionic and methylmalonic acidemia): low-protein diet limited in substances that metabolize into propionyl-CoA: **V**aline, **O**dd-chain fatty acids, **M**ethionine, **I**soleucine, **T**hreonine (**VOMIT**).

### Glycogen regulation by insulin and glucagon/epinephrine




| | |
|---|---|
| **Glycogen** | Branches have α-(1,6) bonds; linkages have α-(1,4) bonds. |
| **Skeletal muscle** | Glycogen undergoes glycogenolysis → glucose-1-phosphate → glucose-6-phosphate, which is rapidly metabolized during exercise. |
| **Hepatocytes** | Glycogen is stored and undergoes glycogenolysis to maintain blood sugar at appropriate levels. Glycogen phosphorylase ❹ liberates glucose-1-phosphate residues off branched glycogen until 4 glucose units remain on a branch. Then 4-α-D-glucanotransferase (debranching enzyme ❺) moves 3 of the 4 glucose units from the branch to the linkage. Then α-1,6-glucosidase (debranching enzyme ❻) cleaves off the last residue, liberating glucose. “Limit dextrin” refers to the two to four residues remaining on a branch after glycogen phosphorylase has already shortened it. |




Note: A small amount of glycogen is degraded in lysosomes by ❼ α-1,4-glucosidase (acid maltase).

**Glycogen storage diseases**

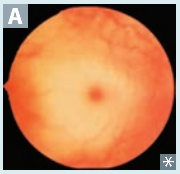
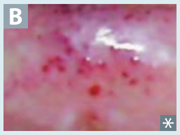
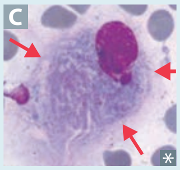
At least 15 types have been identified, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells. Periodic acid–Schiff stain identifies glycogen and is useful in identifying these diseases.

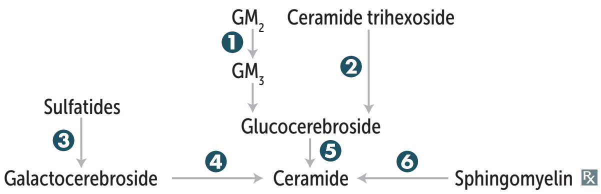
Vice president can't accept money. Types I-V are autosomal recessive. Andersen: Branching. Cori: Debranching. (ABCD)

| DISEASE | FINDINGS | DEFICIENT ENZYME | COMMENTS |
|---|---|---|---|
| **Von Gierke disease (type I)** | Severe fasting hypoglycemia, ↑↑ Glycogen in liver and kidneys, ↑ blood lactate, ↑ triglycerides, ↑ uric acid (Gout), and hepatomegaly, renomegaly. Liver does not regulate blood glucose. | Glucose-6-phosphatase. | Treatment: frequent oral glucose/cornstarch; avoidance of fructose and galactose.<br>Impaired gluconeogenesis and glycogenolysis. |
| **Pompe disease (type II)** | Cardiomyopathy, hypotonia, exercise intolerance, and systemic findings lead to early death. | Lysosomal acid α-1,4-glucosidase (acid maltase) with α-1,6-glucosidase activity. | Pompe trashes the pump (1st and 4th letter; heart, liver, and muscle). |
| **Cori disease (type III)** | Similar to von Gierke disease, but milder symptoms and normal blood lactate levels. Can lead to cardiomyopathy. Limit dextrin–like structures accumulate in cytosol. | Debranching enzymes (α-1,6-glucosidase and 4-α-D-glucanotransferase). | Gluconeogenesis is intact. |
| **Andersen disease (type IV)** | Most commonly presents with hepatosplenomegaly and failure to thrive in early infancy.<br>Other findings include infantile cirrhosis, muscular weakness, hypotonia, cardiomyopathy early childhood death. | Branching enzyme.<br>Neuromuscular form can present at any age. | Hypoglycemia occurs late in the disease. |
| **McArdle disease (type V)** | ↑ glycogen in muscle, but muscle cannot break it down → painful muscle cramps, myoglobinuria (red urine) with strenuous exercise, and arrhythmia from electrolyte abnormalities. Second-wind phenomenon noted during exercise due to ↑ muscular blood flow. | Skeletal muscle glycogen phosphorylase (myophosphorylase).<br>Characterized by a flat venous lactate curve with normal rise in ammonia levels during exercise. | Blood glucose levels typically unaffected.<br>McArdle = muscle. |

**Lysosomal storage diseases**

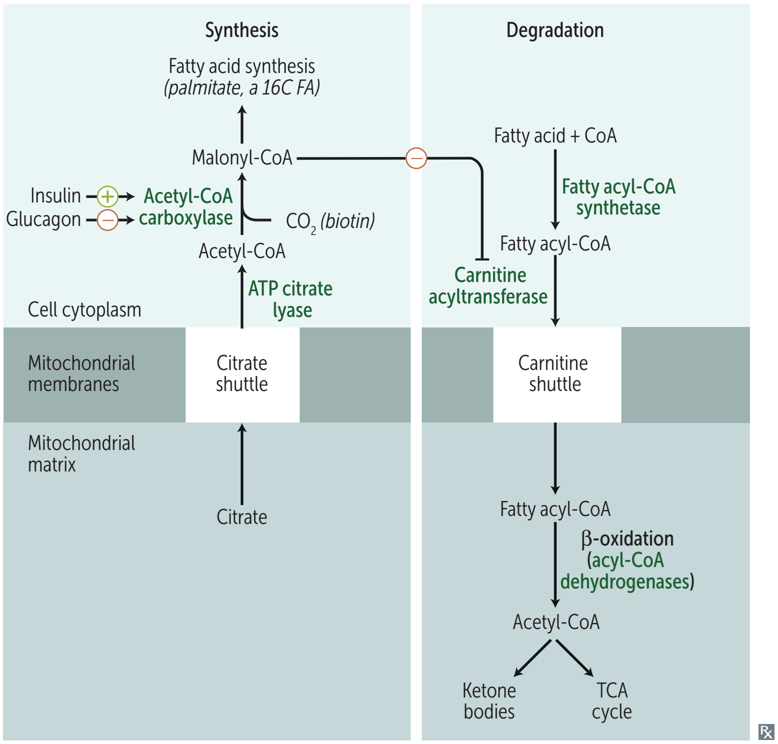
Lysosomal enzyme deficiency → accumulation of abnormal metabolic products. ↑ incidence of Tay-Sachs, Niemann-Pick, and some forms of Gaucher disease in Ashkenazi Jews.

| DISEASE | FINDINGS | DEFICIENT ENZYME | ACCUMULATED SUBSTRATE | INHERITANCE |
|---|---|---|---|---|
| **Sphingolipidoses** | | | | |
| **Tay-Sachs disease** A  | Progressive neurodegeneration, developmental delay, hyperreflexia, hyperacusis, "cherry-red" spot on macula A (lipid accumulation in ganglion cell layer), lysosomes with onion skin, no hepatosplenomegaly (vs Niemann-Pick). | ❶ Hexosaminidase A ("TAy-Sax"). | $GM_2$ ganglioside. | AR |
| **Fabry disease** B  | Early: triad of episodic peripheral neuropathy, angiokeratomas B, hypohidrosis. Late: progressive renal failure, cardiovascular disease. | ❷ α-galactosidase A. | Ceramide trihexoside (globotriaosylceramide). | XR |
| **Metachromatic leukodystrophy** | Central and peripheral demyelination with ataxia, dementia. | ❸ Arylsulfatase A. | Cerebroside sulfate. | AR |
| **Krabbe disease** | Peripheral neuropathy, destruction of oligodendrocytes, developmental delay, optic atrophy, globoid cells. | ❹ Galactocerebrosidase (galactosylceramidase). | Galactocerebroside, psychosine. | AR |
| **Gaucher disease** C  | Most common. Hepatosplenomegaly, pancytopenia, osteoporosis, avascular necrosis of femur, bone crises, Gaucher cells C (lipid-laden macrophages resembling crumpled tissue paper). | ❺ Glucocerebrosidase (β-glucosidase); treat with recombinant glucocerebrosidase. | Glucocerebroside. | AR |
| **Niemann-Pick disease** D  | Progressive neurodegeneration, hepatosplenomegaly, foam cells (lipid-laden macrophages) D, "cherry-red" spot on macula A. | ❻ Sphingomyelinase. | Sphingomyelin. | AR |
| **Mucopolysaccharidoses** | | | | |
| **Hurler syndrome** | Developmental delay, skeletal abnormalities, airway obstruction, corneal clouding, hepatosplenomegaly. | α-L-iduronidase. | Heparan sulfate, dermatan sulfate. | AR |
| **Hunter syndrome** | Mild Hurler + aggressive behavior, no corneal clouding. | Iduronate-2 (two)-sulfatase. | Heparan sulfate, dermatan sulfate. | XR |




Hunters see clearly (no corneal clouding) and aggressively aim for the X (X-linked recessive).

## Fatty acid metabolism




Fatty acid synthesis requires transport of citrate from mitochondria to cytosol. Predominantly occurs in liver, lactating mammary glands, and adipose tissue.

Long-chain fatty acid (LCFA) degradation requires carnitine-dependent transport into the mitochondrial matrix.

"**Sy**trate" = **sy**nthesis.
**Car**nitine = **car**nage of fatty acids.

**Systemic 1° carnitine deficiency**—no cellular uptake of carnitine → no transport of LCFAs into mitochondria → toxic accumulation of LCFAs in the cytosol. Causes weakness, hypotonia, hypoketotic hypoglycemia, dilated cardiomyopathy.

**Medium-chain acyl-CoA dehydrogenase deficiency**—↓ ability to break down fatty acids into acetyl-CoA → accumulation of fatty acyl carnitines in the blood with hypoketotic hypoglycemia. Causes vomiting, lethargy, seizures, coma, liver dysfunction, hyperammonemia. Can lead to sudden death in infants or children. Treat by avoiding fasting.

## Ketone bodies

In the liver, fatty acids and amino acids are metabolized to acetoacetate and β-hydroxybutyrate (to be used in muscle and brain).

In prolonged starvation and diabetic ketoacidosis, oxaloacetate is depleted for gluconeogenesis. With chronic alcohol overuse, excess NADH shunts oxaloacetate to malate. All of these processes lead to a buildup of acetyl-CoA, which is shunted into ketone body synthesis.

Ketone bodies: acetone, acetoacetate, β-hydroxybutyrate.

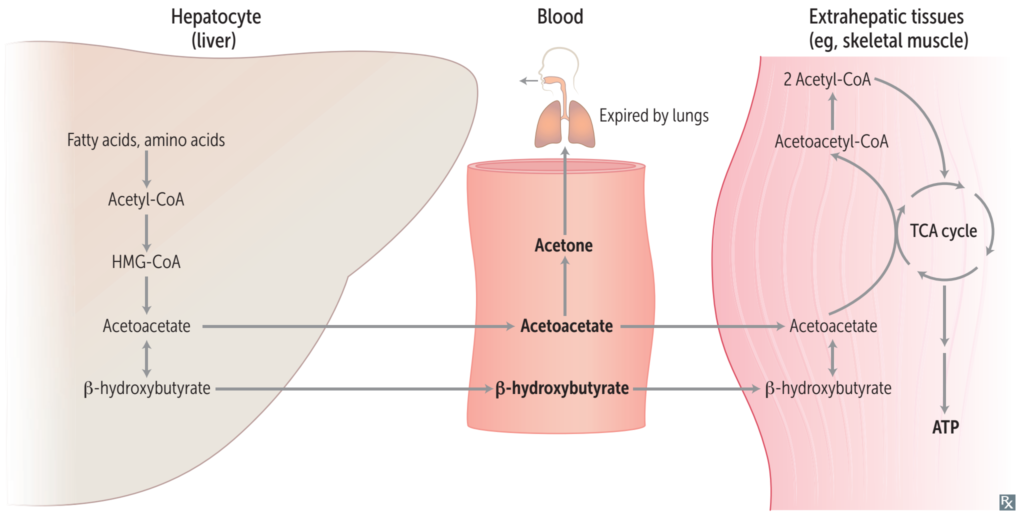
Breath smells like acetone (fruity odor).

Urine test for ketones can detect acetoacetate, but not β-hydroxybutyrate.

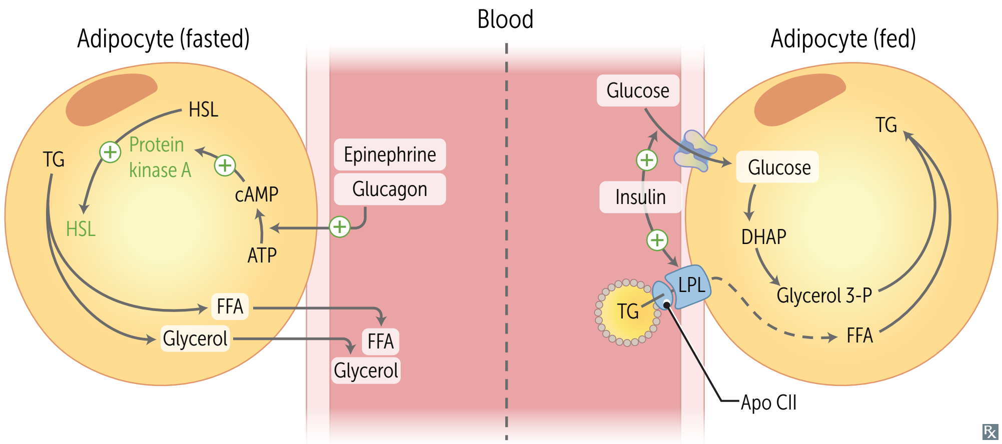
RBCs cannot utilize ketones; they strictly use glucose.

HMG-CoA lyase for ketone production.

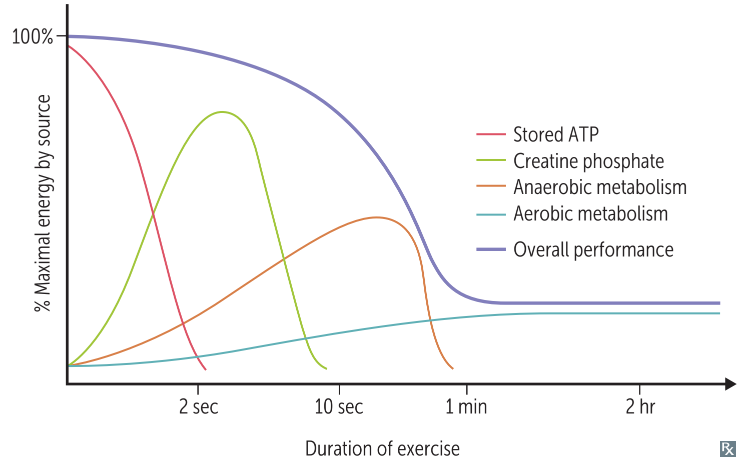
HMG-CoA reductase for cholesterol synthesis.



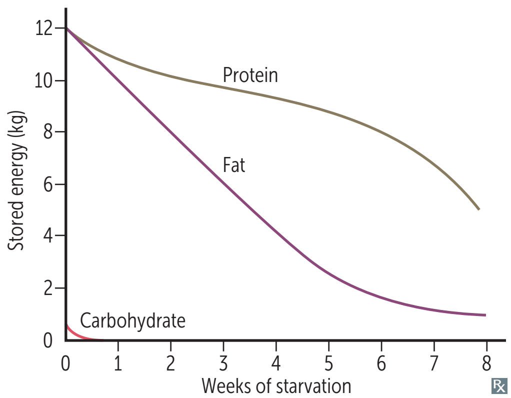

## Fasted vs fed state



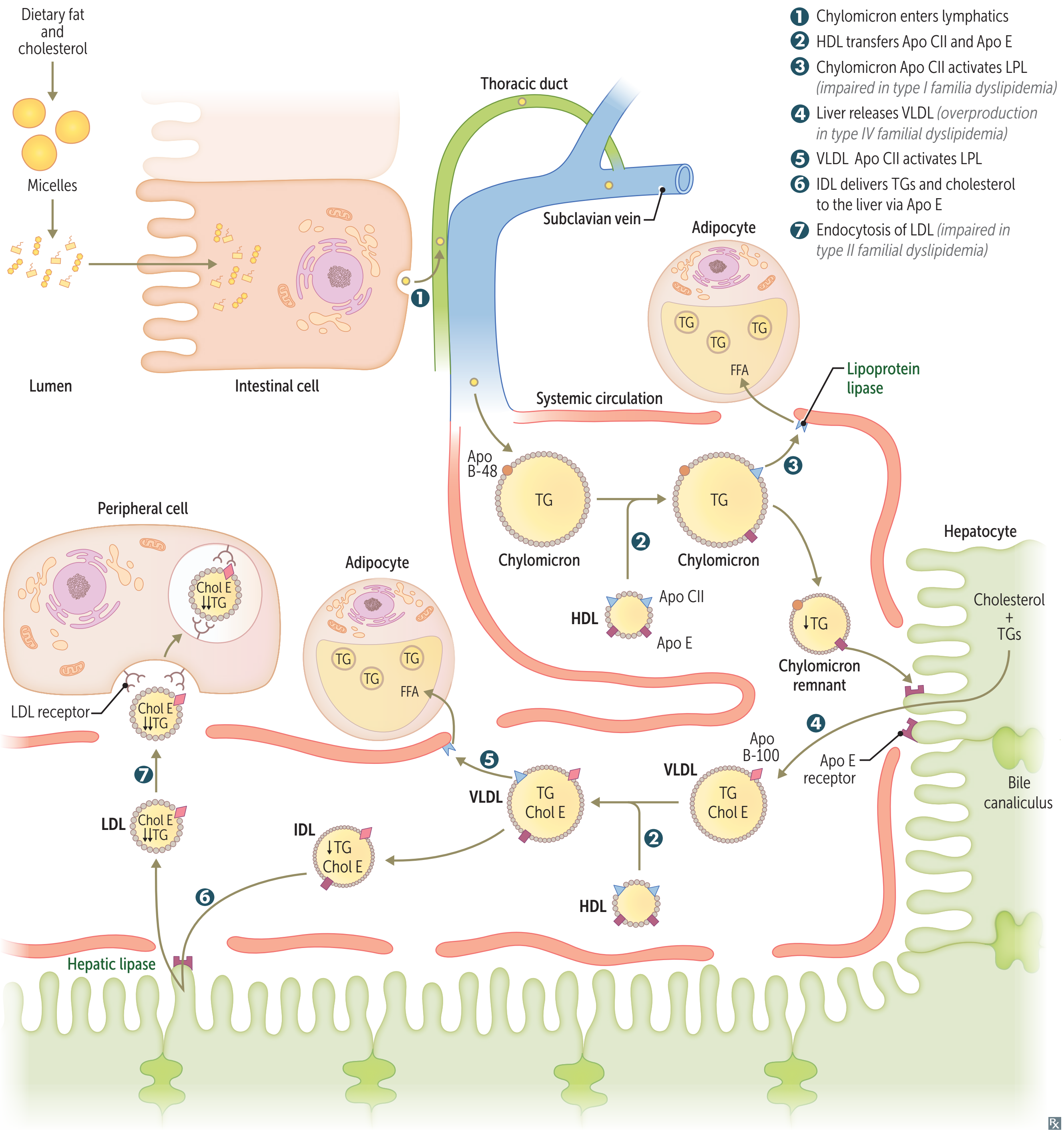
## Metabolic fuel use




1g **carb**/protein = **4** kcal
1g **alcohol** = **7** kcal
1g **fatty acid** = **9** kcal
(# letters = # kcal)

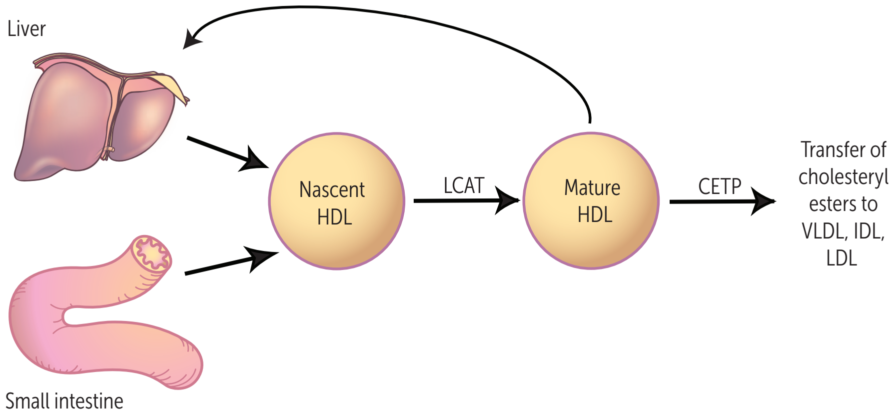
| **Fasting and starvation** | Priorities are to supply sufficient glucose to the brain and RBCs and to preserve protein. | |
|---|---|---|
| Fed state (after a meal) | Glycolysis and aerobic respiration. | Insulin stimulates storage of lipids, proteins, and glycogen. |
| Fasting (between meals) | Hepatic glycogenolysis (major); hepatic gluconeogenesis, adipose release of FFA (minor). | Glucagon and epinephrine stimulate use of fuel reserves. |
| Starvation days 1–3 | Blood glucose levels maintained by:<br>▪ Hepatic glycogenolysis<br>▪ Adipose release of FFA<br>▪ Muscle and liver, which shift fuel use from glucose to FFA<br>▪ Hepatic gluconeogenesis from peripheral tissue lactate and alanine, and from adipose tissue glycerol and propionyl-CoA (from odd-chain FFA—the only triacylglycerol components that contribute to gluconeogenesis) | Glycogen reserves depleted after day 1.<br>RBCs lack mitochondria and therefore cannot use ketones.<br><br> |
| Starvation after day 3 | Adipose stores (ketone bodies become the main source of energy for the brain). After these are depleted, vital protein degradation accelerates, leading to organ failure and death.<br>Amount of excess stores determines survival time. | |

## Lipid transport



## Key enzymes in lipid transport

| | |
|---|---|
| **Cholesteryl ester transfer protein** | Mediates transfer of cholesteryl esters to other lipoprotein particles. |
| **Hepatic lipase** | Degrades TGs remaining in IDL and chylomicron remnants. |
| **Hormone-sensitive lipase** | Degrades TGs stored in adipocytes. Promotes gluconeogenesis by releasing glycerol. |
| **Lecithin-cholesterol acyltransferase** | Catalyzes esterification of ⅔ of plasma cholesterol (ie, required for HDL maturation). |
| **Lipoprotein lipase** | Degrades TGs in circulating chylomicrons. |
| **Pancreatic lipase** | Degrades dietary TGs in small intestine. |
| **PCSK9** | Degrades LDL receptor → ↑ serum LDL. Inhibition → ↑ LDL receptor recycling → ↓ serum LDL. |




## Major apolipoproteins

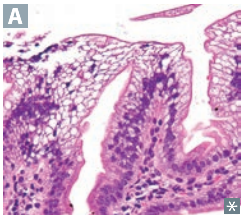
| Apolipoprotein | Function | Chylomicron | Chylomicron remnant | VLDL | IDL | LDL | HDL |
|---|---|---|---|---|---|---|---|
| **E** | Mediates remnant uptake (everything except LDL) | ✓ | ✓ | ✓ | ✓ | | ✓ |
| **A-I** | Found only on alpha-lipoproteins (HDL), activates LCAT | | | | | | ✓ |
| **C-II** | Lipoprotein lipase cofactor that catalyzes cleavage. | ✓ | | ✓ | ✓ | | ✓ |
| **B-48** | Mediates chylomicron secretion into lymphatics<br>Only on particles originating from the intestines | ✓ | ✓ | | | | |
| **B-100** | Binds LDL receptor<br>Only on particles originating from the liver | | | ✓ | ✓ | ✓ | |

**Lipoprotein functions**

Lipoproteins are composed of varying proportions of cholesterol, TGs, and phospholipids. LDL and HDL carry the most cholesterol.
Cholesterol is needed to maintain cell membrane integrity and synthesize bile acids, steroids, and vitamin D.

| | |
|---|---|
| **Chylomicron** | Delivers dietary TGs to peripheral tissues. Delivers cholesterol to liver in the form of chylomicron remnants, which are mostly depleted of their TGs. Secreted by intestinal epithelial cells. |
| **VLDL** | Delivers hepatic TGs to peripheral tissue. Secreted by liver. |
| **IDL** | Delivers TGs and cholesterol to liver. Formed from degradation of VLDL. |
| **LDL** | Delivers hepatic cholesterol to peripheral tissues. Formed by hepatic lipase modification of IDL in the liver and peripheral tissue. Taken up by target cells via receptor-mediated endocytosis. LDL is Lethal. |
| **HDL** | Mediates reverse cholesterol transport from peripheral tissues to liver. Acts as a repository for apolipoproteins C and E (which are needed for chylomicron and VLDL metabolism). Secreted from both liver and intestine. Alcohol ↑ synthesis. HDL is Healthy. |

**Abetalipoproteinemia**




Autosomal recessive. Mutation in gene that encodes microsomal transfer protein (*MTP*). Chylomicrons, VLDL, LDL absent. Deficiency in ApoB-48, ApoB-100. Affected infants present with severe fat malabsorption, steatorrhea, failure to thrive. Later manifestations include retinitis pigmentosa, spinocerebellar degeneration due to vitamin E deficiency, progressive ataxia, acanthocytosis. Intestinal biopsy shows lipid-laden enterocytes A.
Treatment: restriction of long-chain fatty acids, large doses of oral vitamin E.

**Familial dyslipidemias**

| TYPE | INHERITANCE | PATHOGENESIS | ↑ BLOOD LEVEL | CLINICAL |
|---|---|---|---|---|
| **I—Hyper-chylomicronemia** | AR | Lipoprotein lipase or ApoC-2 deficiency | Chylomicrons, TG, cholesterol | Pancreatitis, hepatosplenomegaly, and eruptive/pruritic xanthomas (no ↑ risk for atherosclerosis). Creamy layer in supernatant. |
| **II—Hyper-cholesterolemia** | AD | Absent or defective LDL receptors, or defective ApoB-100 | IIa: LDL, cholesterol<br>IIb: LDL, cholesterol, VLDL | Heterozygotes (1:500) have cholesterol ≈ 300 mg/dL; homozygotes (very rare) have cholesterol ≥ 700 mg/dL.<br>Accelerated atherosclerosis (may have MI before age 20), tendon (Achilles) xanthomas, and corneal arcus. |
| **III—Dysbeta-lipoproteinemia** | AR | ApoE (defective in type thrEE) | Chylomicrons, VLDL | Premature atherosclerosis, tuberoeruptive and palmar xanthomas. ApE's palms. |
| **IV—Hyper-triglyceridemia** | AD | Hepatic overproduction of VLDL | VLDL, TG | Hypertriglyceridemia (> 1000 mg/dL) can cause acute pancreatitis. Related to insulin resistance. |

HIGH-YIELD PRINCIPLES IN

# Immunology

*"I hate to disappoint you, but my rubber lips are immune to your charms."*

—*Batman & Robin*

*"Imagine the action of a vaccine not just in terms of how it affects a single body, but also in terms of how it affects the collective body of a community."*

—Eula Biss

*"Some people are immune to good advice."*

—Saul Goodman, *Breaking Bad*

Learning the components of the immune system and their roles in host defense at the cellular level is essential for both the understanding of disease pathophysiology and clinical practice. Know the immune mechanisms of responses to vaccines. Both congenital and acquired immunodeficiencies are very testable. Cell surface markers are high yield for understanding immune cell interactions and for laboratory diagnosis. Know the roles and functions of major cytokines and chemokines.

## ▸ IMMUNOLOGY—LYMPHOID STRUCTURES

**Immune system organs**

1° organs:
- Bone marrow—immune cell production, B cell maturation
- Thymus—T cell maturation

2° organs:
- Spleen, lymph nodes, tonsils, Peyer patches
- Allow immune cells to interact with antigen

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**Lymph node**

A 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae A B. Functions are nonspecific filtration by macrophages, circulation of B and T cells, and immune response activation.

**Follicle**

Site of B-cell localization and proliferation. In outer cortex. 1° follicles are dense and quiescent. 2° follicles have pale central germinal centers and are active.

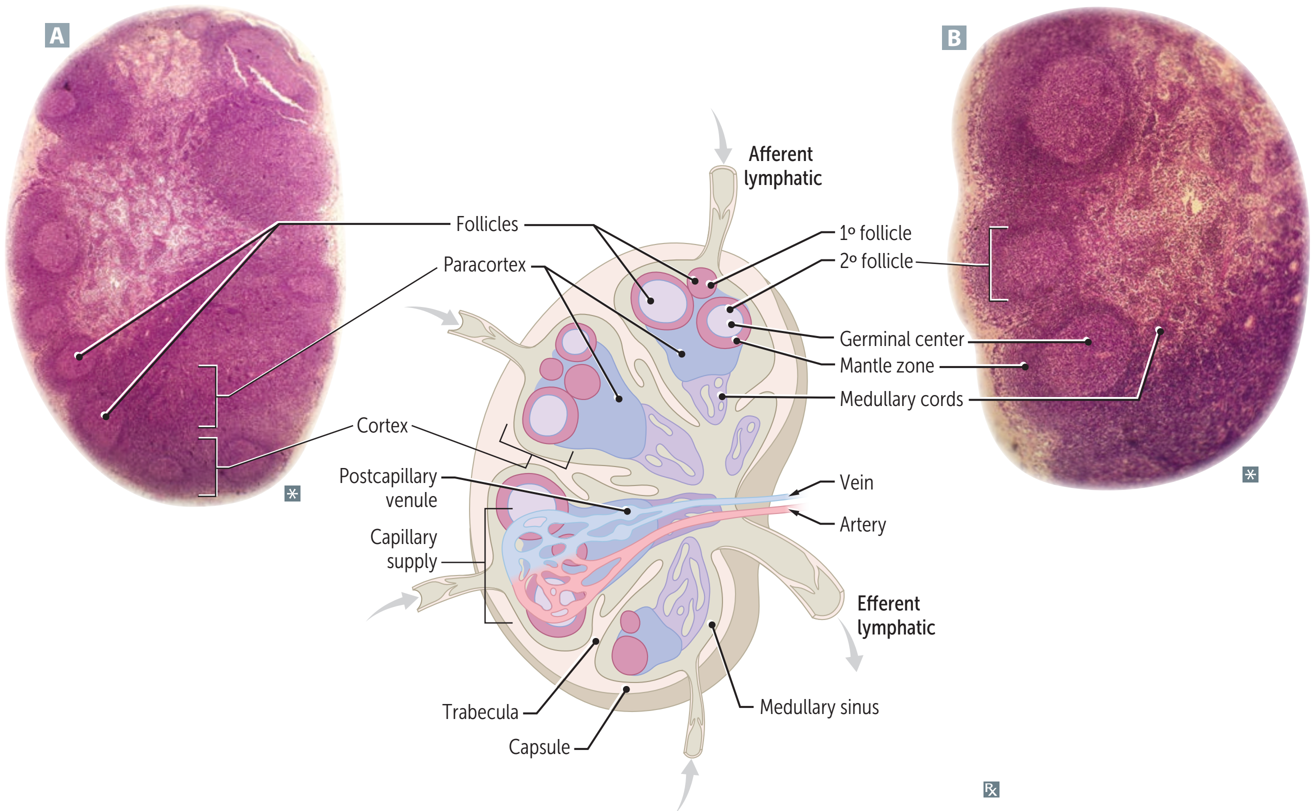
**Medulla**

Consists of medullary cords (closely packed lymphocytes and plasma cells) and medullary sinuses. Medullary sinuses communicate with efferent lymphatics and contain reticular cells and macrophages.

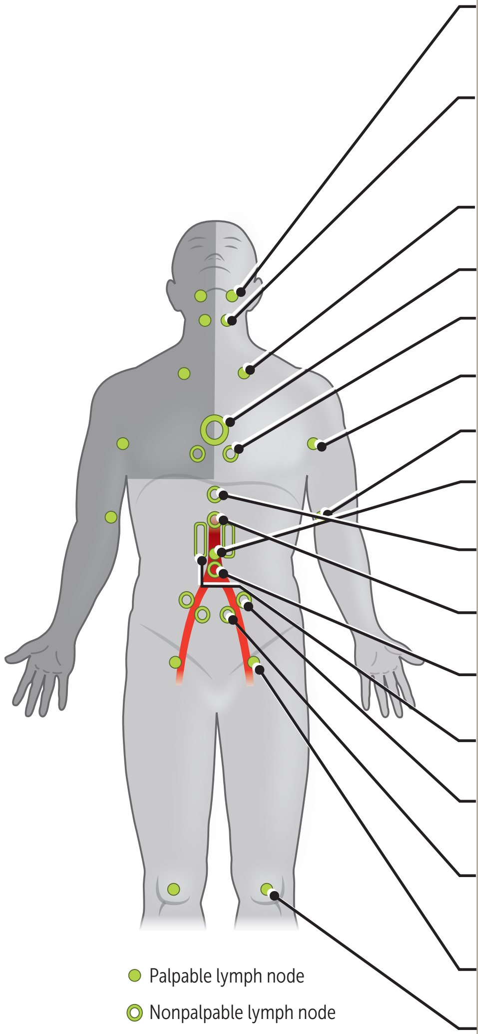
**Paracortex**

Contains T cells. Region of cortex between follicles and medulla. Contains high endothelial venules through which T and B cells enter from blood. Not well developed in patients with DiGeorge syndrome.

Paracortex enlarges in an extreme cellular immune response (eg, EBV and other viral infections → paracortical hyperplasia → lymphadenopathy).



## Lymphatic drainage associations

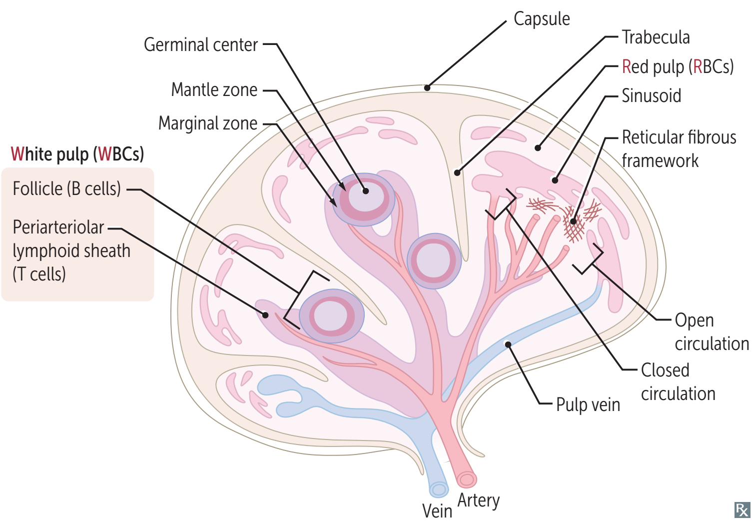



| Lymph node cluster | Area of body drained | Associated pathology |
|---|---|---|
| Submandibular | Oral cavity | Malignancy of oral cavity |
| Deep cervical | Head, neck, oropharynx | Upper respiratory tract infection<br>Infectious mononucleosis<br>Kawasaki disease<br>Malignancy of head, neck, oropharynx |
| Supraclavicular (Virchow node) | Abdomen, pelvis | Malignancy of abdomen, pelvis |
| Mediastinal | Trachea, esophagus | Pulmonary TB (unilateral hilar)<br>Sarcoidosis (bilateral hilar)<br>Lung cancer<br>Granulomatous disease |
| Hilar | Lungs | |
| Axillary | Upper limb, breast, skin above umbilicus | Mastitis<br>Metastasis (especially breast cancer) |
| Epitrochlear | Hand, forearm | Secondary syphilis |
| Periumbilical (Sister Mary Joseph node) | Abdomen, pelvis | Gastric cancer |
| Celiac | Liver, stomach, spleen, pancreas, upper duodenum | Mesenteric lymphadenitis<br>Inflammatory bowel disease<br>Celiac disease |
| Superior mesenteric | Lower duodenum, jejunum, ileum, colon to splenic flexure | |
| Inferior mesenteric | Colon from splenic flexure to upper rectum | |
| Para-aortic | Pair of testes, ovaries, kidneys, fallopian tubes (uterus) | Metastasis |
| External iliac | Cervix, superior bladder, body of uterus | Sexually transmitted infections<br>Medial foot/leg cellulitis (superficial inguinal) |
| Internal iliac | Lower rectum to anal canal (above pectinate line), bladder, vagina (middle third), cervix, prostate | |
| Superficial inguinal | Anal canal (below pectinate line), skin below umbilicus (except popliteal area), scrotum, vulva | |
| Popliteal ("pop-lateral") | Dorsolateral foot, posterior calf | Lateral foot/leg cellulitis |

Right lymphatic duct drains right side of body above diaphragm into junction of the right subclavian and internal jugular vein

Thoracic duct drains below the diaphragm and left thorax and upper limb into junction of left subclavian and internal jugular veins (rupture of thoracic duct can cause chylothorax)

## Spleen




Located in LUQ of abdomen, anterolateral to left kidney, protected by 9th-11th ribs.

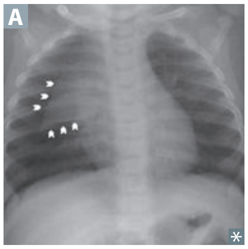
Splenic dysfunction (eg, postsplenectomy, sickle cell disease autosplenectomy) → ↓ IgM → ↓ complement activation → ↓ C3b opsonization → ↑ susceptibility to encapsulated organisms.

Postsplenectomy findings:
- Howell-Jolly bodies (nuclear remnants)
- Target cells
- Thrombocytosis (loss of sequestration and removal)
- Lymphocytosis (loss of sequestration)

Vaccinate patients undergoing splenectomy or with splenic dysfunction against encapsulated organisms (pneumococci, Hib, meningococci).

| | |
|---|---|
| **Periarteriolar lymphatic sheath** | Contains T cells. Located within white pulp. |
| **Follicle** | Contains B cells. Located within white pulp. |
| **Marginal zone** | Contains macrophages and specialized B cells. Site where antigen-presenting cells (APCs) capture blood-borne antigens for recognition by lymphocytes. Located between red pulp and white pulp. |

## Thymus




Located in the anterosuperior mediastinum. Site of T-cell differentiation and maturation. Encapsulated. **Th**ymus epithelium is derived from **th**ird pharyngeal pouch (endoderm), whereas thymic lymphocytes are of mesodermal origin. Cortex is dense with immature T cells; **m**edulla is pale with **m**ature T cells and Hassall corpuscles containing epithelial reticular cells.

Normal neonatal thymus "sail-shaped" on CXR (asterisks in A), involutes by age 3 years.

**T** cells = **T**hymus
**B** cells = **B**one marrow

Absent thymic shadow or hypoplastic thymus seen in some immunodeficiencies (eg, SCID, DiGeorge syndrome).

**Thymoma**—neoplasm of thymus. Associated with myasthenia gravis, superior vena cava syndrome, pure red cell aplasia, Good syndrome.

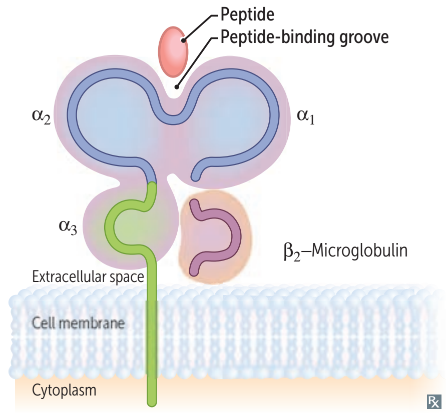
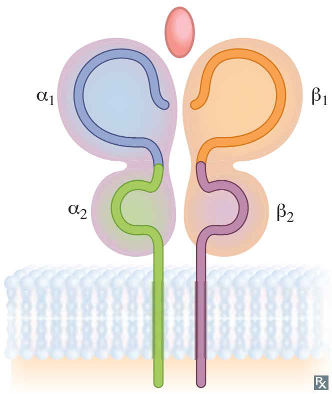
## ▸ IMMUNOLOGY—CELLULAR COMPONENTS

### Innate vs adaptive immunity

| | Innate immunity | Adaptive immunity |
|---|---|---|
| COMPONENTS | Neutrophils, macrophages, monocytes, dendritic cells, natural killer (NK) cells (lymphoid origin), complement, physical epithelial barriers, secreted enzymes | T cells, B cells, circulating antibodies |
| MECHANISM | Germline encoded | Variation through V(D)J recombination during lymphocyte development |
| RESPONSE TO PATHOGENS | Nonspecific<br>Occurs rapidly (minutes to hours)<br>No memory response | Highly specific, refined over time<br>Develops over long periods; memory response is faster and more robust |
| SECRETED PROTEINS | Lysozyme, complement, C-reactive protein (CRP), defensins, cytokines | Immunoglobulins, cytokines |
| KEY FEATURES IN PATHOGEN RECOGNITION | Toll-like receptors (TLRs): pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs) and lead to activation of NF-κB. Examples of PAMPs: LPS (gram ⊖ bacteria), flagellin (bacteria), nucleic acids (viruses) | Memory cells: activated B and T cells; subsequent exposure to a previously encountered antigen → stronger, quicker immune response |

## Major histocompatibility complex I and II

MHC encoded by HLA genes. Present antigen fragments to T cells and bind T-cell receptors (TCRs).

| | MHC I | MHC II |
|---|---|---|
| LOCI | HLA-**A**, HLA-**B**, HLA-**C**<br>MHC **I** loci have **1** letter | HLA-**DP**, HLA-**DQ**, HLA-**DR**<br>MHC **II** loci have **2** letters |
| BINDING | TCR and CD8 | TCR and CD4 |
| STRUCTURE | **1** long chain, **1** short chain | **2** equal-length chains (**2** α, **2** β) |
| EXPRESSION | All nucleated cells, APCs, platelets (except RBCs) | APCs |
| FUNCTION | Present endogenous antigens (eg, viral or cytosolic proteins) to CD8+ cytotoxic T cells | Present exogenous antigens (eg, bacterial proteins) to CD4+ helper T cells |
| ANTIGEN LOADING | Antigen peptides loaded onto MHC I in RER after delivery via TAP (transporter associated with antigen processing) | Antigen loaded following release of invariant chain in an acidified endosome |
| ASSOCIATED PROTEINS | $\beta_2$-microglobulin | Invariant chain |
| STRUCTURE |  |  |





## HLA subtypes associated with diseases

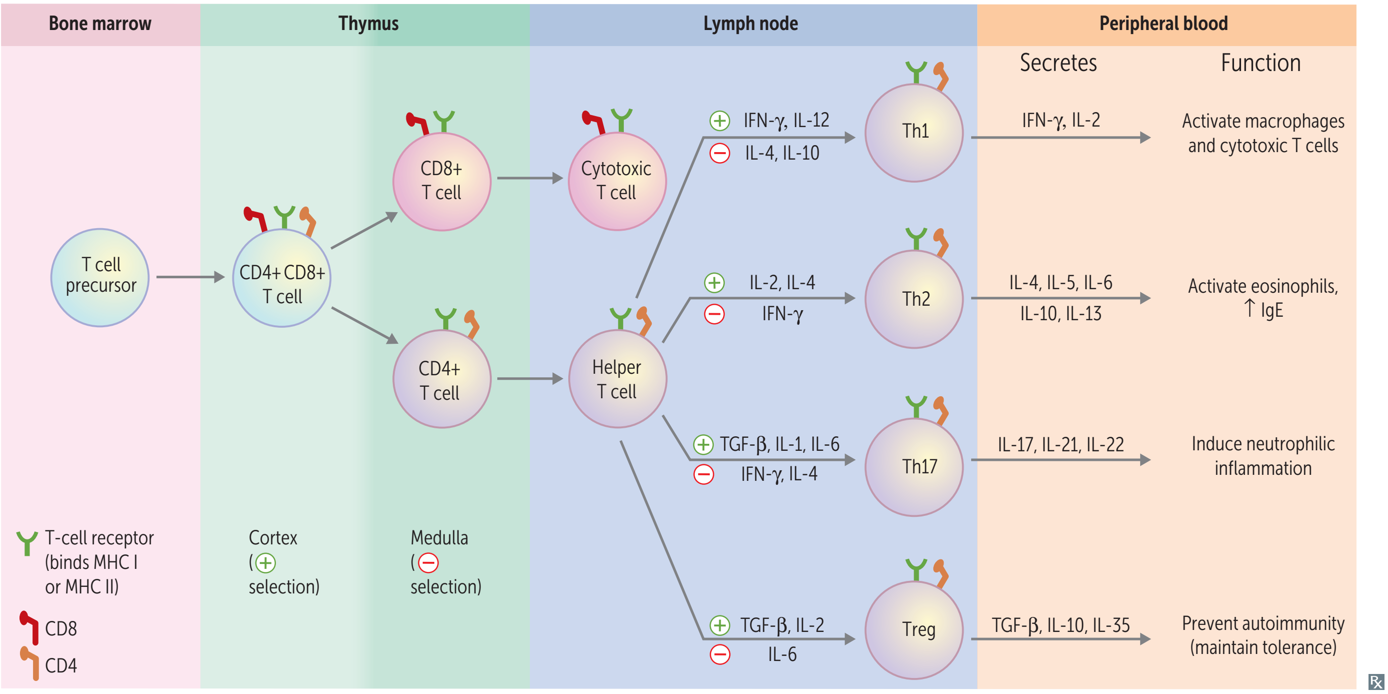
| HLA SUBTYPE | DISEASE | MNEMONIC |
|---|---|---|
| **B27** | **P**soriatic arthritis, **A**nkylosing spondylitis, **I**BD-associated arthritis, **R**eactive arthritis | **PAIR.** Also called seronegative arthropathies |
| **B57** | Abacavir hypersensitivity | |
| **DQ2/DQ8** | Celiac disease | I ate (8) too (2) much gluten at **D**airy **Q**ueen |
| **DR3** | DM type 1, **SLE**, Graves disease, Hashimoto thyroiditis, Addison disease | **2-3**, **S-L-E**<br>DM type **1**: HLA-**3** and -**4** (1 + 3 = 4) |
| **DR4** | **Rheum**atoid arthritis, DM type **1**, Addison disease | There are **4** walls in **1** "**rheum**" (room) |

| | |
|---|---|
| **Functions of natural killer cells** | Lymphocyte member of innate immune system.<br>Use perforin and granzymes to induce apoptosis of virally infected cells and tumor cells.<br>Activity enhanced by IL-2, IL-12, IFN-α, and IFN-β.<br>Induced to kill when exposed to a nonspecific activation signal on target cell and/or to an absence of an inhibitory signal such as MHC I on target cell surface.<br>Also kills via antibody-dependent cell-mediated cytotoxicity (CD16 binds Fc region of bound IgG, activating the NK cell). |

## Major functions of B and T cells

| | |
|---|---|
| **B cells** | Humoral immunity.<br>Recognize and present antigen—undergo somatic hypermutation to optimize antigen specificity.<br>Produce antibody—differentiate into plasma cells to secrete specific immunoglobulins.<br>Maintain immunologic memory—memory B cells persist and accelerate future response to antigen. |
| **T cells** | Cell-mediated immunity.<br>CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes.<br>CD8+ T cells directly kill virus-infected and tumor cells via perforin and granzymes (similar to NK cells).<br>Delayed cell-mediated hypersensitivity (type IV).<br>Acute and chronic cellular organ rejection.<br>**Rule of 8**: MHC **II** × CD4 = 8; MHC **I** × CD8 = 8. |

## Differentiation of T cells

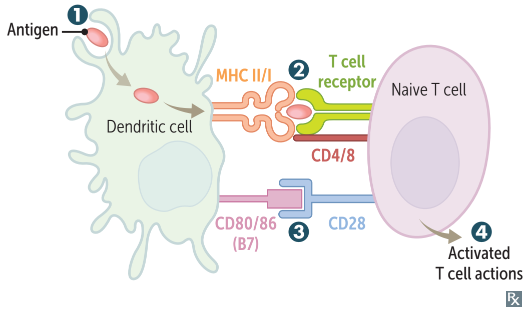



| | |
|---|---|
| **Positive selection** | Thymic cortex. T cells expressing TCRs capable of binding self-MHC on cortical epithelial cells survive. |
| **Negative selection** | Thymic medulla. T cells expressing TCRs with high affinity for self antigens undergo apoptosis or become regulatory T cells. Tissue-restricted self-antigens are expressed in the thymus due to the action of autoimmune regulator (**AIRE**); deficiency leads to autoimmune polyendocrine syndrome-1 (**C**hronic mucocutaneous candidiasis, **H**ypoparathyroidism, **A**drenal insufficiency, **R**ecurrent *Candida* infections). "Without **AIRE**, your body will **CHAR**". |
| **Macrophage-lymphocyte interaction** | Th1 cells secrete IFN-γ, which enhances the ability of monocytes and macrophages to kill microbes they ingest. This function is also enhanced by interaction of T cell CD40L with CD40 on macrophages. Macrophages also activate lymphocytes via antigen presentation. |
| **Cytotoxic T cells** | Kill virus-infected, neoplastic, and donor graft cells by inducing apoptosis.<br>Release cytotoxic granules containing preformed proteins (eg, perforin, granzyme B).<br>Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells. |
| **Regulatory T cells** | Help maintain specific immune tolerance by suppressing $CD4^+$ and $CD8^+$ T-cell effector functions.<br>Identified by expression of CD3, CD4, CD25, and FOXP3.<br>Activated regulatory T cells (Tregs) produce anti-inflammatory cytokines (eg, IL-10, TGF-β).<br>**IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome**—genetic deficiency of FOXP3 → autoimmunity. Characterized by enteropathy, endocrinopathy, nail dystrophy, dermatitis, and/or other autoimmune dermatologic conditions. Associated with diabetes in male infants. |

**T- and B-cell activation** APCs: B cells, dendritic cells, Langerhans cells, macrophages.
Two signals are required for T-cell activation, B-cell activation, and class switching.

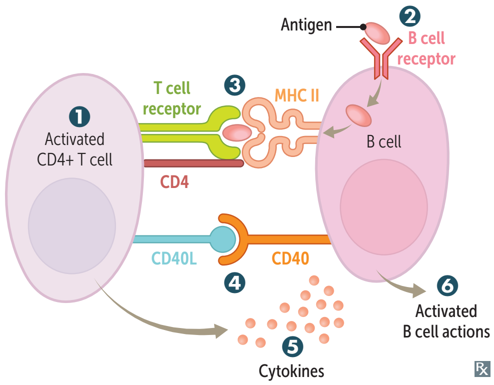
**T-cell activation**

❶ Dendritic cell (specialized APC) ingests and processes antigen, then migrates to the draining lymph node.
❷ T-cell activation (signal 1): exogenous antigen is presented on MHC II and recognized by TCR on Th (CD4+) cell. Endogenous or cross-presented antigen is presented on MHC I to Tc (CD8+) cell.
❸ Proliferation and survival (signal 2): costimulatory signal via interaction of B7 protein (CD80/86) on dendritic cell and CD28 on naïve T cell.
❹ Activated Th cell produces cytokines. Tc cell able to recognize and kill virus-infected cell.




**B-cell activation and class switching**

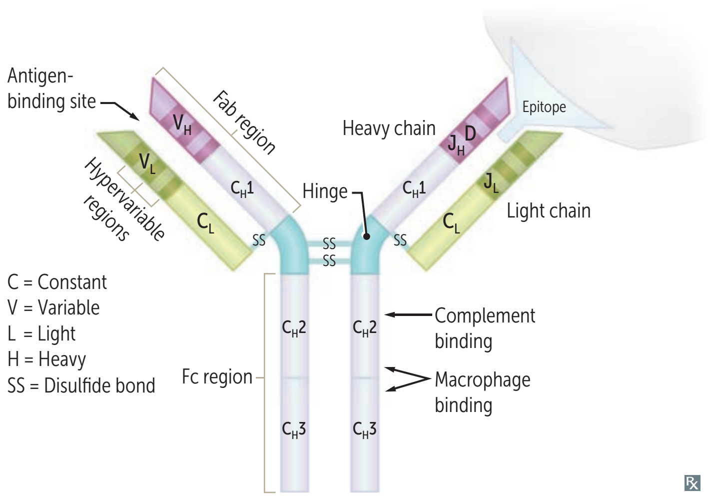
❶ Th-cell activation as above.
❷ B-cell receptor–mediated endocytosis.
❸ Exogenous antigen is presented on MHC II and recognized by TCR on Th cell.
❹ CD40 receptor on B cell binds CD40 ligand (CD40L) on Th cell.
❺ Th cells secrete cytokines that determine Ig class switching of B cells.
❻ B cells are activated and produce IgM. They undergo class switching and affinity maturation.

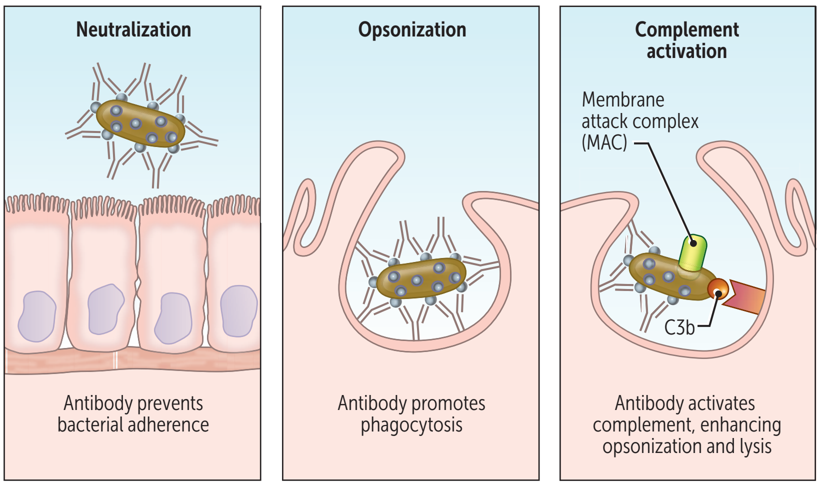


## ▶ IMMUNOLOGY—IMMUNE RESPONSES

### Antibody structure and function

Fab fragment consisting of light (L) and heavy (H) chains recognizes antigens. Fc region of IgM and IgG fixes complement. Heavy chain contributes to Fc and Fab regions. Light chain contributes only to Fab region.



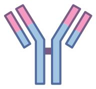
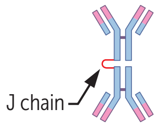
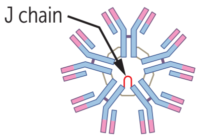
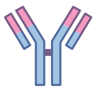
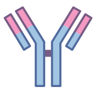

**Fab**:
- **F**ragment, **a**ntigen **b**inding
- Determines idiotype: unique antigen-binding pocket; only 1 antigenic specificity expressed per B cell

**Fc** (**5 C**'s):
- **C**onstant
- **C**arboxy terminal
- **C**omplement binding
- **C**arbohydrate side chains
- **C**onfers (determines) isotype (IgM, IgD, etc)

**Generation of antibody diversity** (antigen independent)
1. Random recombination of VJ (light-chain) or V(D)J (heavy-chain) genes
2. Random addition of nucleotides to DNA during recombination by terminal deoxynucleotidyl transferase (TdT)
3. Random combination of heavy chains with light chains

**Generation of antibody specificity** (antigen dependent)

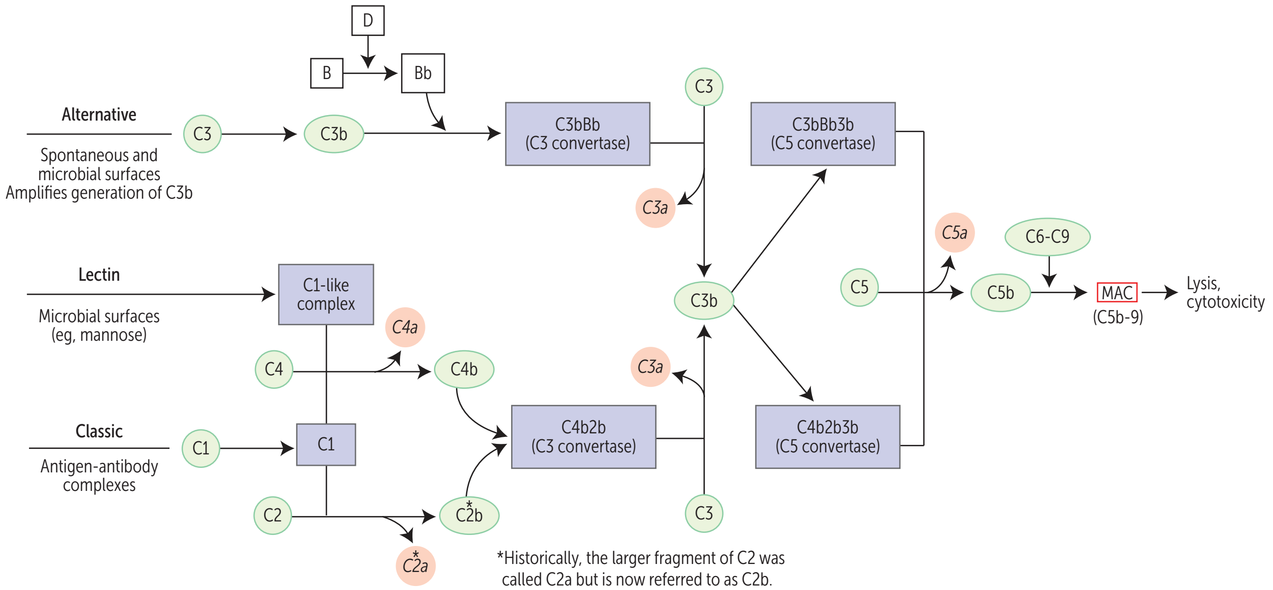
4. Somatic hypermutation and affinity maturation (variable region)
5. Isotype switching (constant region)

| | |
|---|---|
| **Immunoglobulin isotypes** | All isotypes can exist as monomers. Mature, naïve B cells prior to activation express IgM and IgD on their surfaces. They may differentiate in germinal centers of lymph nodes by isotype switching (gene rearrangement; induced by cytokines and CD40L) into plasma cells that secrete IgA, IgE, or IgG.<br>Affinity refers to the individual antibody-antigen interaction, while avidity describes the cumulative binding strength of all antibody-antigen interactions in a multivalent molecule. |
| **IgG**  | Main antibody in 2° response to an antigen. Most abundant isotype in serum. Fixes complement, opsonizes bacteria, neutralizes bacterial toxins and viruses. Only isotype that crosses the placenta (provides infants with passive immunity that starts to wane after birth). "Ig**G** **G**reets the **G**rowing fetus." Associated with **warm** autoimmune hemolytic anemia ("**warm** weather is **G**reat!"). |
| **IgA**   | Prevents attachment of bacteria and viruses to mucous membranes; does not fix complement. Monomer (in circulation) or dimer (with J chain when secreted). Crosses epithelial cells by transcytosis. Produced in GI tract (eg, by Peyer patches) and protects against gut infections (eg, *Giardia*). Most produced antibody overall, but has lower serum concentrations. Released into secretions (tears, saliva, mucus) and breast milk. Picks up secretory component from epithelial cells, which protects the Fc portion from luminal proteases. |
| **IgM**   | Produced in the 1° (**IM**mediate) response to an antigen. Fixes complement. Antigen receptor on the surface of B cells. Monomer on B cell, pentamer with J chain when secreted. Pentamer enables avid binding to antigen while humoral response evolves. Associated with cold autoimmune hemolytic anemia. |
| **IgD**  | Unclear function. Found on surface of many B cells and in serum. |
| **IgE**  | Binds mast cells and basophils; cross-links when exposed to allergen, mediating immediate (type I) hypersensitivity through release of inflammatory mediators such as histamine. Contributes to immunity to parasites by activating **E**osinophils. |

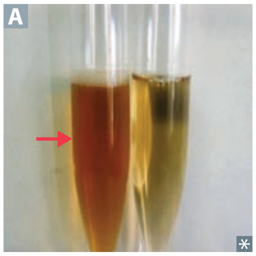
## Antigen type and memory

| | |
|---|---|
| **Thymus-independent antigens** | Antigens lacking a peptide component (eg, lipopolysaccharides from gram ⊖ bacteria); cannot be presented by MHC to T cells. Weakly immunogenic; vaccines often require boosters and adjuvants (eg, capsular polysaccharide subunit of *Streptococcus pneumoniae* PPSV23 vaccine). |
| **Thymus-dependent antigens** | Antigens containing a protein component (eg, diphtheria toxoid). Class switching and immunologic memory occur as a result of direct contact of B cells with Th cells. |

| | | |
|---|---|---|
| **Complement** | System of hepatically synthesized plasma proteins that play a role in innate immunity and inflammation. Membrane attack complex (MAC) defends against gram ⊖ bacteria. The $CH_{50}$ test is used to screen for activation of the classical complement pathway. | |
| ACTIVATION PATHWAYS | **Classic**—Ig**G** or Ig**M** mediated.<br>Alternative—microbe surface molecules.<br>Lectin—mannose or other sugars on microbe surface. | **GM** makes **classic** cars. |
| FUNCTIONS | C3b—opsonization.<br>C3**a**, C4**a**, C5**a**—**a**naphylaxis.<br>C5a—neutrophil chemotaxis.<br>C**5b-9** (MAC)—cytolysis. | C3**b** **b**inds to lipopolysaccharides on **b**acteria.<br>**MAC** complex is important for neutralizing ***Neis**seria* species. Deficiency results in recurrent infection.<br>Get "**Neis**" (nice) Big **MAC**s from **5-9** pm. |
| | **Opsonins**—C3b and IgG are the two 1° opsonins in bacterial defense; enhance phagocytosis. C3b also helps clear immune complexes. | *Opsonin* (Greek) = to prepare for eating. |
| | **Inhibitors**—decay-accelerating factor (DAF, aka CD55) and C1 esterase inhibitor help prevent complement activation on self cells (eg, RBCs). | |



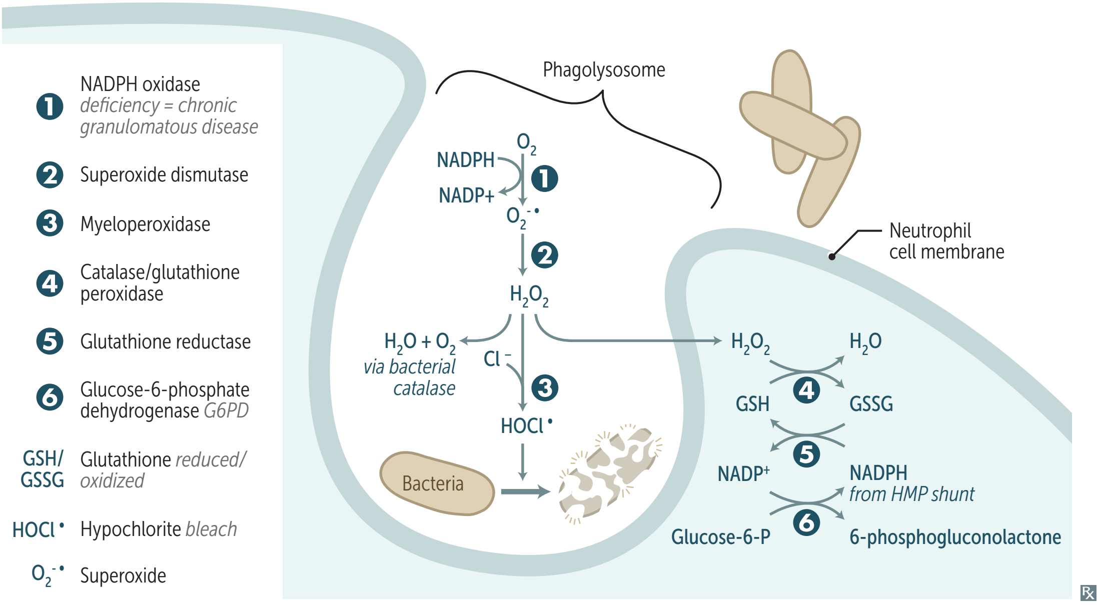
## Complement disorders

| Complement protein deficiencies | |
|---|---|
| **Early complement deficiencies (C1-C4)** | ↑ risk of severe, recurrent pyogenic sinus and respiratory tract infections. C3b used in clearance of antigen-antibody complexes → ↑ risk of **SLE** (think **SLEarly**). |
| **Terminal complement deficiencies (C5–C9)** | ↑ susceptibility to recurrent *Neisseria* bacteremia. |
| **Complement regulatory protein deficiencies** | |
| **C1 esterase inhibitor deficiency** | Causes hereditary angioedema due to unregulated activation of kallikrein → ↑ bradykinin. Characterized by ↓ C4 levels. ACE inhibitors are contraindicated (also ↑ bradykinin). |
| **Paroxysmal nocturnal hemoglobinuria**  | A defect in the *PIGA* gene prevents the formation of glycosylphosphatidylinositol (GPI) anchors for complement inhibitors, such as decay-accelerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59). Causes complement-mediated intravascular hemolysis → ↓ haptoglobin, dark urine A. Can cause atypical venous thrombosis (eg, Budd-Chiari syndrome; portal vein, cerebral, or dermal thrombosis). |

| **Important cytokines** | Acute (IL-1, IL-6, TNF-α), then recruit (IL-8, IL-12). | |
|---|---|---|
| SECRETED BY MACROPHAGES | | |
| **Interleukin-1** | Causes fever, acute inflammation. Activates endothelium to express adhesion molecules. Induces chemokine secretion to recruit WBCs. Also called osteoclast-activating factor. | "**Hot T-bone stEAK**":<br>IL-1: fever (**hot**).<br>IL-2: stimulates **T** cells.<br>IL-3: stimulates **bone** marrow.<br>IL-4: stimulates Ig**E** production.<br>IL-5: stimulates Ig**A** production.<br>IL-6: stimulates a**K**ute-phase protein production. |
| **Interleukin-6** | Causes fever and stimulates production of acute-phase proteins. | |
| **Tumor necrosis factor-α** | Activates endothelium. Causes WBC recruitment, vascular leak. | Causes cachexia in malignancy.<br>Maintains granulomas in TB.<br>IL-1, IL-6, TNF-α can mediate fever and sepsis. |
| **Interleukin-8** | Major chemotactic factor for neutrophils. | "**Clean up** on **aisle 8**." Neutrophils are recruited by **IL-8** to **clear** infections. |
| **Interleukin-12** | Induces differentiation of T cells into Th1 cells. Activates NK cells. | Facilitates granuloma formation in TB. |
| SECRETED BY T CELLS | | |
| **Interleukin-2** | Stimulates growth of helper, cytotoxic, and regulatory T cells, and NK cells. | |
| **Interleukin-3** | Supports growth and differentiation of bone marrow stem cells. Functions like GM-CSF. | |
| FROM Th1 CELLS | | |
| **Interferon-γ** | Secreted by NK cells and T cells in response to antigen or IL-12 from macrophages; stimulates macrophages to kill phagocytosed pathogens. Inhibits differentiation of Th2 cells.<br>Induces IgG isotype switching in B cells. | Also activates NK cells to kill virus-infected cells. Increases MHC expression and antigen presentation by all cells. Activates macrophages to induce granuloma formation. |
| FROM Th2 CELLS | | |
| **Interleukin-4** | Induces differentiation of T cells into Th (**help**er) **2** cells. Promotes growth of **B** cells. Enhances class switching to Ig**E** and Ig**G**. | Ain't too proud **2 BEG 4 help**. |
| **Interleukin-5** | Promotes growth and differentiation of **B** cells. Enhances class switching to Ig**A**. Stimulates growth and differentiation of **E**osinophils. | I have **5 BAE**s. |
| **Interleukin-10** | Attenuates inflammatory response. Decreases expression of MHC class II and Th1 cytokines. Inhibits activated macrophages and dendritic cells. Also secreted by regulatory T cells. | TGF-**β** and IL-**10** **b**oth at**ten**uate the immune response. |
| **Interleukin-13** | Promotes IgE production by B cells. Induces alternative macrophage activation. | |

**Respiratory burst**

Also called oxidative burst. Involves the activation of the phagocyte NADPH oxidase complex (eg, in neutrophils, monocytes), which utilizes $O_2$ as a substrate. Plays an important role in the immune response → rapid release of reactive oxygen species (ROS). NADPH plays a role in both the creation and neutralization of ROS. Myeloperoxidase contains a blue-green, heme-containing pigment that gives sputum its color.




Phagocytes of patients with CGD can utilize $H_2O_2$ generated by invading organisms and convert it to ROS. Patients are at ↑ risk for infection by catalase ⊕ species (eg, *S aureus*, *Aspergillus*) capable of neutralizing their own $H_2O_2$, leaving phagocytes without ROS for fighting infections.

Pyocyanin of *P aeruginosa* generates ROS to kill competing pathogens. Oxidative burst also leads to $K^+$ influx, which releases lysosomal enzymes. Lactoferrin is a protein found in secretory fluids and neutrophils that inhibits microbial growth via iron chelation.

**Interferons** IFN-α, IFN-β, IFN-γ

| | |
|---|---|
| MECHANISM | A part of innate host defense, interferons interfere with both RNA and DNA viruses. Cells infected with a virus synthesize these glycoproteins, which act on local cells, priming them for viral defense by downregulating protein synthesis to resist potential viral replication and by upregulating MHC expression to facilitate recognition of infected cells. Also play a major role in activating antitumor immunity. |
| CLINICAL USE | Chronic HBV, Kaposi sarcoma, hairy cell leukemia, condyloma acuminatum, renal cell carcinoma, malignant melanoma, multiple sclerosis, chronic granulomatous disease. |
| ADVERSE EFFECTS | Flu-like symptoms, depression, neutropenia, myopathy, interferon-induced autoimmunity. |

## Cell surface proteins

| | | |
|---|---|---|
| **T cells** | TCR (binds antigen-MHC complex)<br>CD3 (associated with TCR for signal transduction)<br>CD28 (binds B7 on APC) | |
| Helper T cells | CD4, CD40L, CXCR4/CCR5 (co-receptors for HIV) | |
| Cytotoxic T cells | CD8 | |
| Regulatory T cells | CD4, CD25 | |
| **B cells** | Ig (binds antigen)<br>CD19, CD20, CD21 (receptor for Epstein-Barr virus), CD40<br>MHC II, B7 | Must be 21 to drink Beer in a Barr |
| **Macrophages** | CD14 (receptor for PAMPs, eg, LPS), CD40<br>CCR5<br>MHC II, B7 (CD80/86)<br>Fc and C3b receptors (enhanced phagocytosis) | |
| **NK cells** | CD16 (binds Fc of IgG), CD56 (suggestive marker for NK) | |
| **Hematopoietic stem cells** | CD34 | |

**Anergy** State during which a cell cannot become activated by exposure to its antigen. T and B cells become anergic when exposed to their antigen without costimulatory signal (signal 2). Another mechanism of self-tolerance.

## Passive vs active immunity

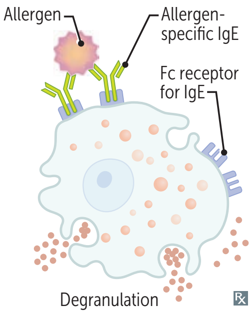
| | Passive | Active |
|---|---|---|
| MEANS OF ACQUISITION | Receiving preformed antibodies | Exposure to exogenous antigens |
| ONSET | Rapid | Slow |
| DURATION | Short span of antibodies (half-life = 3 weeks) | Long-lasting protection (memory) |
| EXAMPLES | IgA in breast milk, maternal IgG crossing placenta, antitoxin, humanized monoclonal antibody | Natural infection, vaccines, toxoid |
| NOTES | After exposure to tetanus toxin, HBV, varicella, rabies virus, botulinum toxin, or diphtheria toxin, unvaccinated patients are given preformed antibodies (passive)—"to Heal very rapidly before dying" | Combined passive and active immunizations can be given for hepatitis B or rabies exposure |

**Vaccination** Induces an active immune response (humoral and/or cellular) to specific pathogens.

| VACCINE TYPE | DESCRIPTION | PROS/CONS | EXAMPLES |
|---|---|---|---|
| **Live attenuated vaccine** | Microorganism rendered nonpathogenic but retains capacity for transient growth within inoculated host. Induces **cellular and humoral responses.** MMR and varicella vaccines can be given to people living with HIV without evidence of immunity if CD4 cell count ≥ 200 cells/mm$^3$. | Pros: induces strong, often lifelong immunity.<br>Cons: may revert to virulent form. Contraindicated in pregnant and immunodeficient patients. | **A**denovirus (nonattenuated, given to military recruits), **t**yphoid (Ty21a, oral), **p**olio (Sabin), **v**aricella (chickenpox), **small**pox, **B**CG, **y**ellow fever, **inf**luenza (intranasal), **MMR**, **r**otavirus.<br>"**A**ttention **t**eachers! **P**lease **v**accinate **small**, **B**eautiful **y**oung **inf**ants with **MMR** **r**egularly!" |
| **Killed or inactivated vaccine** | Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response. Mainly induces a **humoral response.** | Pros: safer than live vaccines.<br>Cons: weaker immune response; booster shots usually required. | Hepatitis **A**, **T**yphoid (Vi polysaccharide, intramuscular), **R**abies, **I**nfluenza, **P**olio (Sal**K**).<br>**A TRIP** could **K**ill you. |
| **Subunit** | Includes only the antigens that best stimulate the immune system. | Pros: lower chance of adverse reactions.<br>Cons: expensive, weaker immune response. | HBV (antigen = HBsAg), HPV (types 6, 11, 16, and 18), acellular pertussis (aP), *Neisseria meningitidis* (various strains), *Streptococcus pneumoniae*, *Haemophilus influenzae* type b. |
| **Toxoid** | Denatured bacterial toxin with an intact receptor binding site. Stimulates the immune system to make antibodies without potential for causing disease. | Pros: protects against the bacterial toxins.<br>Cons: antitoxin levels decrease with time, may require a booster. | *Clostridium tetani*, *Corynebacterium diphtheriae*. |

**Hypersensitivity types** Four types (**ABCD**): **A**naphylactic and **A**topic (type I), Anti**B**ody-mediated (type II), Immune **C**omplex (type III), **D**elayed (cell-mediated, type IV). Types I, II, and III are all antibody-mediated.

## Type I hypersensitivity




Anaphylactic and atopic—two phases:

- Immediate (minutes): antigen crosslinks preformed IgE on presensitized mast cells → immediate degranulation → release of histamine (a vasoactive amine), tryptase (marker of mast cell activation), and leukotrienes.
- Late (hours): chemokines (attract inflammatory cells, eg, eosinophils) and other mediators from mast cells → inflammation and tissue damage.

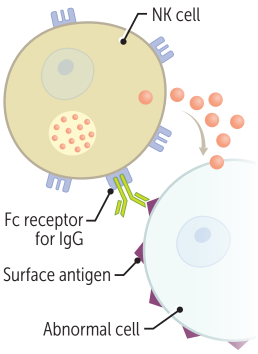
**F**irst (type) and **F**ast (anaphylaxis).

Test: skin test or blood test (ELISA) for allergen-specific IgE.

Example:

- Anaphylaxis (eg, food, drug, or bee sting allergies)
- Allergic asthma

## Type II hypersensitivity




Antibody-dependent cellular cytotoxicity

Antibodies bind to cell-surface antigens → cellular destruction, inflammation, and cellular dysfunction.

**Direct** Coombs test—detects antibodies attached **direct**ly to the RBC surface.
Indirect Coombs test—detects presence of unbound antibodies in the serum.

Cellular destruction—cell is opsonized (coated) by antibodies, leading to either:

- Phagocytosis and/or activation of complement system.
- NK cell killing (antibody-dependent cellular cytotoxicity).

Examples:

- Autoimmune hemolytic anemia (including drug-induced form)
- Immune thrombocytopenia
- Transfusion reactions
- Hemolytic disease of the newborn

Inflammation—binding of antibodies to cell surfaces → activation of complement system and Fc receptor-mediated inflammation.

Examples:

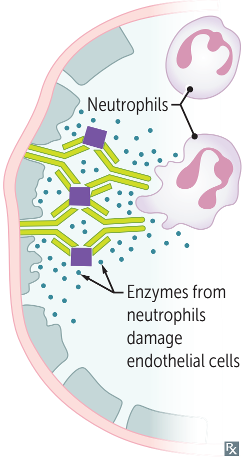
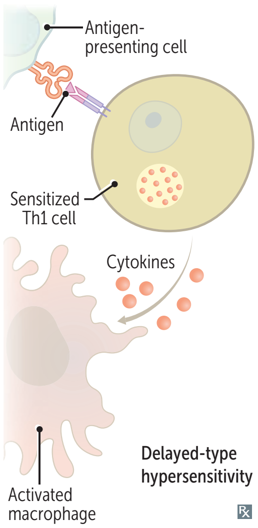
- Goodpasture syndrome
- Rheumatic fever
- Hyperacute transplant rejection

Cellular dysfunction—antibodies bind to cell surface receptors → abnormal blockade or activation of downstream process.

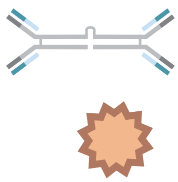
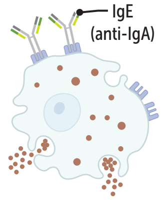
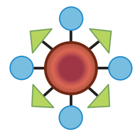
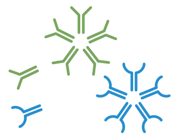
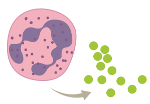
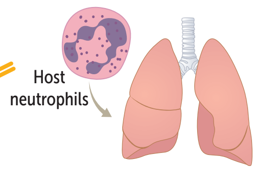
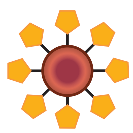
Examples:

- Myasthenia gravis
- Graves disease
- Pemphigus vulgaris

### Hypersensitivity types *(continued)*

| | | |
|---|---|---|
| **Type III hypersensitivity**   | Immune complex—antigen-antibody (mostly IgG) complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes.<br>Can be associated with vasculitis and systemic manifestations. | In type **III** reaction, imagine an immune complex as **3** things stuck together: antigen-antibody-complement.<br>Examples:<br>▪ SLE<br>▪ Rheumatoid arthritis<br>▪ Reactive arthritis<br>▪ Polyarteritis nodosa<br>▪ Poststreptococcal glomerulonephritis |
| | **Serum sickness**—the prototypic immune complex disease. Antibodies to foreign proteins are produced and 1–2 weeks later, antibody-antigen complexes form and deposit in tissues → complement activation → inflammation and tissue damage (↓ serum C3, C4). | Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 1–2 weeks after antigen exposure. Serum sickness-like reactions are associated with some drugs (may act as haptens, eg, penicillin, monoclonal antibodies) and infections (eg, hepatitis B). |
| | **Arthus reaction**—a local subacute immune complex-mediated hypersensitivity reaction. Intradermal injection of antigen into a presensitized (has circulating IgG) individual leads to immune complex formation in the skin (eg, enhanced local reaction to a booster vaccination). Characterized by edema, fibrinoid necrosis, activation of complement. | |
| **Type IV hypersensitivity**   | Two mechanisms, each involving T cells:<br>1. Direct cell cytotoxicity: CD8+ cytotoxic T cells kill targeted cells.<br>2. Inflammatory reaction: effector CD4+ T cells recognize antigen and release inflammation-inducing cytokines (shown in illustration). | Response does not involve antibodies (vs types I, II, and III).<br>Examples:<br>▪ Contact dermatitis (eg, poison ivy, nickel allergy)<br>▪ Graft-versus-host disease<br>Tests: PPD for TB infection; patch test for contact dermatitis; *Candida* skin test for T cell immune function.<br>4**T**'s: **T** cells, **T**ransplant rejections, **T**B skin tests, **T**ouching (contact dermatitis).<br><br>**Fourth** (type) and **last** (delayed). |

## Blood transfusion reactions

| TYPE | PATHOGENESIS | TIMING | CLINICAL PRESENTATION | DONOR BLOOD | HOST BLOOD |
|---|---|---|---|---|---|
| **Allergic/ anaphylactic reaction** | Type I hypersensitivity reaction against plasma proteins in transfused blood<br>IgA-deficient individuals should receive blood products without IgA | Within minutes to 2-3 hr (due to release of preformed inflammatory mediators in degranulating mast cells) | Allergies: urticaria, pruritus<br>Anaphylaxis: wheezing, hypotension, respiratory arrest, shock | <br>Donor plasma proteins, including IgA | <br>Host mast cell |
| **Acute hemolytic transfusion reaction** | Type II hypersensitivity reaction<br>Typically causes intravascular hemolysis (ABO blood group incompatibility) | During transfusion or within 24 hr (due to preformed antibodies) | Fever, hypotension, tachypnea, tachycardia, flank pain, hemoglobinuria (intravascular), jaundice (extravascular) | <br>Donor RBC with A and/ or B group antigens | <br>Host anti-A, anti-B IgG, IgM |
| **Febrile nonhemolytic transfusion reaction** | Cytokines created by donor WBCs accumulate during storage of blood products<br>Reactions prevented by leukoreduction of blood products | Within 1-6 hr (due to preformed cytokines) | Fever, headaches, chills, flushing<br>More common in children | <br>Donor WBC releases preformed cytokines | |
| **Transfusion-related acute lung injury** | Two-hit mechanism:<br>▪ Neutrophils are sequestered and primed in pulmonary vasculature due to recipient risk factors<br>▪ Neutrophils are activated by a product (eg, antileukocyte antibodies) in the transfused blood and release inflammatory mediators → ↑ capillary permeability → pulmonary edema | Within minutes to 6 hr | Respiratory distress, noncardiogenic pulmonary edema | <br>Donor antileukocyte IgG |  |
| **Delayed hemolytic transfusion reaction** | Anamnestic response to a foreign antigen on donor RBCs (Rh [D] or other minor blood group antigens) previously encountered by recipient<br>Typically causes extravascular hemolysis | Onset over 24 hr<br>Usually presents within 1-2 wk (due to slow destruction by reticuloendothelial system) | Generally self limited and clinically silent<br>Mild fever, hyperbilirubinemia | <br>Donor RBC with foreign antigens | <br>Host IgG |

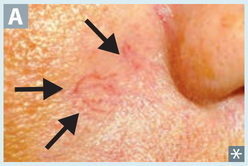
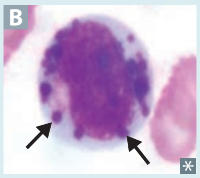
## Autoantibodies

| AUTOANTIBODY | ASSOCIATED DISORDER |
|---|---|
| Anti-postsynaptic ACh receptor | Myasthenia gravis |
| Anti-presynaptic voltage-gated calcium channel | Lambert-Eaton myasthenic syndrome |
| Anti-$\beta_2$ glycoprotein I | Antiphospholipid syndrome |
| Antinuclear (ANA) | Nonspecific screening antibody, often associated with SLE |
| Anticardiolipin, lupus anticoagulant | SLE, antiphospholipid syndrome |
| Anti-dsDNA, anti-Smith | SLE |
| Antihistone | Drug-induced lupus |
| Anti-U1 RNP (ribonucleoprotein) | Mixed connective tissue disease |
| Rheumatoid factor (IgM antibody against IgG Fc region), anti-CCP (more specific) | Rheumatoid arthritis |
| Anti-Ro/SSA, anti-La/SSB | Sjögren syndrome |
| Anti-Scl-70 (anti-DNA topoisomerase I) | Scleroderma (diffuse) |
| Anticentromere | Limited scleroderma (CREST syndrome) |
| Antisynthetase (eg, anti-Jo-1), anti-SRP, anti-helicase (anti-Mi-2) | Polymyositis, dermatomyositis |
| Antimitochondrial | 1° biliary cholangitis |
| Anti-smooth muscle, anti-liver/kidney microsomal-1 | Autoimmune hepatitis |
| Myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)/perinuclear ANCA (p-ANCA) | Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, ulcerative colitis, 1° sclerosing cholangitis |
| PR3-ANCA/cytoplasmic ANCA (c-ANCA) | Granulomatosis with polyangiitis |
| Anti-phospholipase $A_2$ receptor | 1° membranous nephropathy |
| Anti-hemidesmosome | Bullous pemphigoid |
| Anti-desmoglein (anti-desmosome) | Pemphigus vulgaris |
| Antithyroglobulin, antithyroid peroxidase (antimicrosomal) | Hashimoto thyroiditis |
| Anti-TSH receptor | Graves disease |
| IgA anti-endomysial, IgA anti-tissue transglutaminase, IgA and IgG deamidated gliadin peptide | Celiac disease |
| Anti-glutamic acid decarboxylase, islet cell cytoplasmic antibodies | Type 1 diabetes mellitus |
| Antiparietal cell, anti-intrinsic factor | Pernicious anemia |
| Anti-glomerular basement membrane | Goodpasture syndrome |

## Immunodeficiencies

| DISEASE | DEFECT | PRESENTATION | FINDINGS |
|---|---|---|---|
| **B-cell disorders** | | | |
| **X-linked (Bruton) agammaglobulinemia** | Defect in *BTK*, a tyrosine kinase gene → no B-cell maturation; X-linked recessive (↑ in Boys) | Recurrent bacterial and enteroviral infections after 6 months (↓ maternal IgG) | Absent B cells in peripheral blood, ↓ Ig of all classes.<br>Absent/scanty lymph nodes and tonsils (1° follicles and germinal centers absent) → live vaccines contraindicated |
| **Selective IgA deficiency** | Cause unknown<br>Most common 1° immunodeficiency | Majority Asymptomatic<br>Can see Airway and GI infections, Autoimmune disease, Atopy, Anaphylaxis to IgA in blood products | ↓ IgA with normal IgG, IgM levels<br>↑ susceptibility to giardiasis<br>Can cause false-negative celiac disease test |
| **Common variable immunodeficiency** | Defect in B-cell differentiation. Cause unknown in most cases | May present in childhood but usually diagnosed after puberty<br>↑ risk of autoimmune disease, bronchiectasis, lymphoma, sinopulmonary infections | ↓ plasma cells, ↓ immunoglobulins |
| **T-cell disorders** | | | |
| **Thymic aplasia** | 22q11 microdeletion; failure to develop 3rd and 4th pharyngeal pouches → absent thymus and parathyroids<br>DiGeorge syndrome—thymic, parathyroid, cardiac defects<br>Velocardiofacial syndrome—palate, facial, cardiac defects | CATCH-22: Cardiac defects (conotruncal abnormalities [eg, tetralogy of Fallot, truncus arteriosus]), Abnormal facies, Thymic hypoplasia → T-cell deficiency (recurrent viral/fungal infections), Cleft palate, Hypocalcemia 2° to parathyroid aplasia → tetany | ↓ T cells, ↓ PTH, ↓ $Ca^{2+}$<br>Thymic shadow absent on CXR |
| **IL-12 receptor deficiency** | ↓ Th1 response; autosomal recessive | Disseminated mycobacterial and fungal infections; may present after administration of BCG vaccine | ↓ IFN-γ<br>Most common cause of Mendelian susceptibility to mycobacterial diseases (MSMD) |
| **Autosomal dominant hyper-IgE syndrome (Job syndrome)** | Deficiency of Th17 cells due to *STAT3* mutation → impaired recruitment of neutrophils to sites of infection | Cold (noninflamed) staphylococcal Abscesses, retained Baby teeth, Coarse facies, Dermatologic problems (eczema), ↑ IgE, bone Fractures from minor trauma | ↑ IgE<br>↑ eosinophils<br>Learn the ABCDEF's to get a Job! |
| **Chronic mucocutaneous candidiasis** | T-cell dysfunction<br>Impaired cell-mediated immunity against *Candida* sp<br>Classic form caused by defects in *AIRE* | Persistent noninvasive *Candida albicans* infections of skin and mucous membranes | Absent in vitro T-cell proliferation in response to *Candida* antigens<br>Absent cutaneous reaction to *Candida* antigens |

### Immunodeficiencies *(continued)*

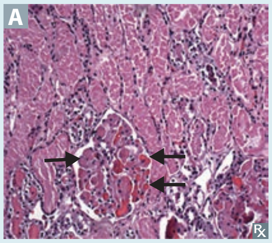
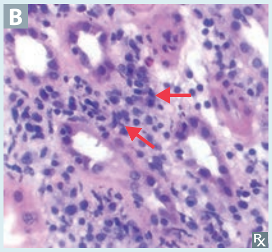
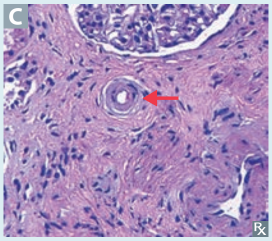
| DISEASE | DEFECT | PRESENTATION | FINDINGS |
|---|---|---|---|
| **B- and T-cell disorders** | | | |
| **Severe combined immunodeficiency** | Several types including defective IL-2R gamma chain (most common, X-linked recessive); adenosine deaminase deficiency (autosomal recessive); *RAG* mutation → VDJ recombination defect | Failure to thrive, chronic diarrhea, thrush<br>Recurrent viral, bacterial, fungal, and protozoal infections | ↓ T-cell receptor excision circles (TRECs)<br>Part of newborn screening for SCID<br>Absence of thymic shadow (CXR), germinal centers (lymph node biopsy), and T cells (flow cytometry) |
| **Ataxia-telangiectasia**<br>A  | Defects in *ATM* gene → failure to detect DNA damage → failure to halt progression of cell cycle → mutations accumulate; autosomal recessive | Triad: cerebellar defects (**A**taxia), spider **A**ngiomas (telangiectasia A), Ig**A** deficiency<br>↑↑ sensitivity to radiation (limit x-ray exposure) | ↑ AFP<br>↓ IgA, IgG, and IgE<br>Lymphopenia, cerebellar atrophy<br>↑ risk of lymphoma and leukemia |
| **Hyper-IgM syndrome** | Most commonly due to defective CD40L on Th cells → class switching defect; X-linked recessive | Severe pyogenic infections early in life; opportunistic infection with *Pneumocystis*, *Cryptosporidium*, CMV | Normal or ↑ IgM<br>↓↓ IgG, IgA, IgE<br>Failure to make germinal centers |
| **Wiskott-Aldrich syndrome** | Mutation in *WAS* gene; leukocytes and platelets unable to reorganize actin cytoskeleton → defective antigen presentation; X-linked recessive | **WATER**: **W**iskott-**A**ldrich: **T**hrombocytopenia, **E**czema, **R**ecurrent (pyogenic) infections<br>↑ risk of autoimmune disease and malignancy | ↓ to normal IgG, IgM<br>↑ IgE, IgA<br>Fewer and smaller platelets |
| **Phagocyte dysfunction** | | | |
| **Leukocyte adhesion deficiency (type 1)** | Defect in LFA-1 integrin (CD18) protein on phagocytes; impaired migration and chemotaxis; autosomal recessive | **L**ate separation (>30 days) of umbilical cord, **a**bsent pus, **d**ysfunctional neutrophils → recurrent skin and mucosal bacterial infections | ↑ neutrophils in blood<br>Absence of neutrophils at infection sites → impaired wound healing |
| **Chédiak-Higashi syndrome**<br>B  | Defect in lysosomal trafficking regulator gene (*LYST*)<br>Microtubule dysfunction in phagosome-lysosome fusion; autosomal recessive | **PLAIN**: **P**rogressive neurodegeneration, **L**ymphohistiocytosis, **A**lbinism (partial), recurrent pyogenic **I**nfections, peripheral **N**europathy | Giant granules (B, arrows) in granulocytes and platelets<br>Pancytopenia<br>Mild coagulation defects |
| **Chronic granulomatous disease** | Defect of NADPH oxidase → ↓ reactive oxygen species (eg, superoxide) and ↓ respiratory burst in neutrophils; X-linked form most common | ↑ susceptibility to catalase ⊕ organisms<br>Recurrent infections and granulomas | Abnormal dihydrorhodamine (flow cytometry) test (↓ green fluorescence)<br>Nitroblue tetrazolium dye reduction test (obsolete) fails to turn blue |

### Infections in immunodeficiency

| PATHOGEN | ↓ T CELLS | ↓ B CELLS | ↓ GRANULOCYTES | ↓ COMPLEMENT |
|---|---|---|---|---|
| **Bacteria** | Sepsis | Encapsulated (Please SHINE my SKiS): *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Haemophilus Influenzae* type b, *Neisseria meningitidis*, *Escherichia coli*, *Salmonella*, *Klebsiella pneumoniae*, group B *Streptococcus* | Some Bacteria Produce No Serious granules: *Staphylococcus*, *Burkholderia cepacia*, *Pseudomonas aeruginosa*, *Nocardia*, *Serratia* | Encapsulated species with early complement deficiencies<br>*Neisseria* with late complement (C5–C9) deficiencies |
| **Viruses** | CMV, EBV, JC virus, VZV, chronic infection with respiratory/GI viruses | Enteroviral encephalitis, poliovirus (live vaccine contraindicated) | N/A | N/A |
| **Fungi/parasites** | *Candida* (local), PCP, *Cryptococcus* | GI giardiasis (no IgA) | *Candida* (systemic), *Aspergillus*, *Mucor* | N/A |

Note: B-cell deficiencies tend to produce recurrent bacterial infections, whereas T-cell deficiencies produce more fungal and viral infections.

### Transplant rejection

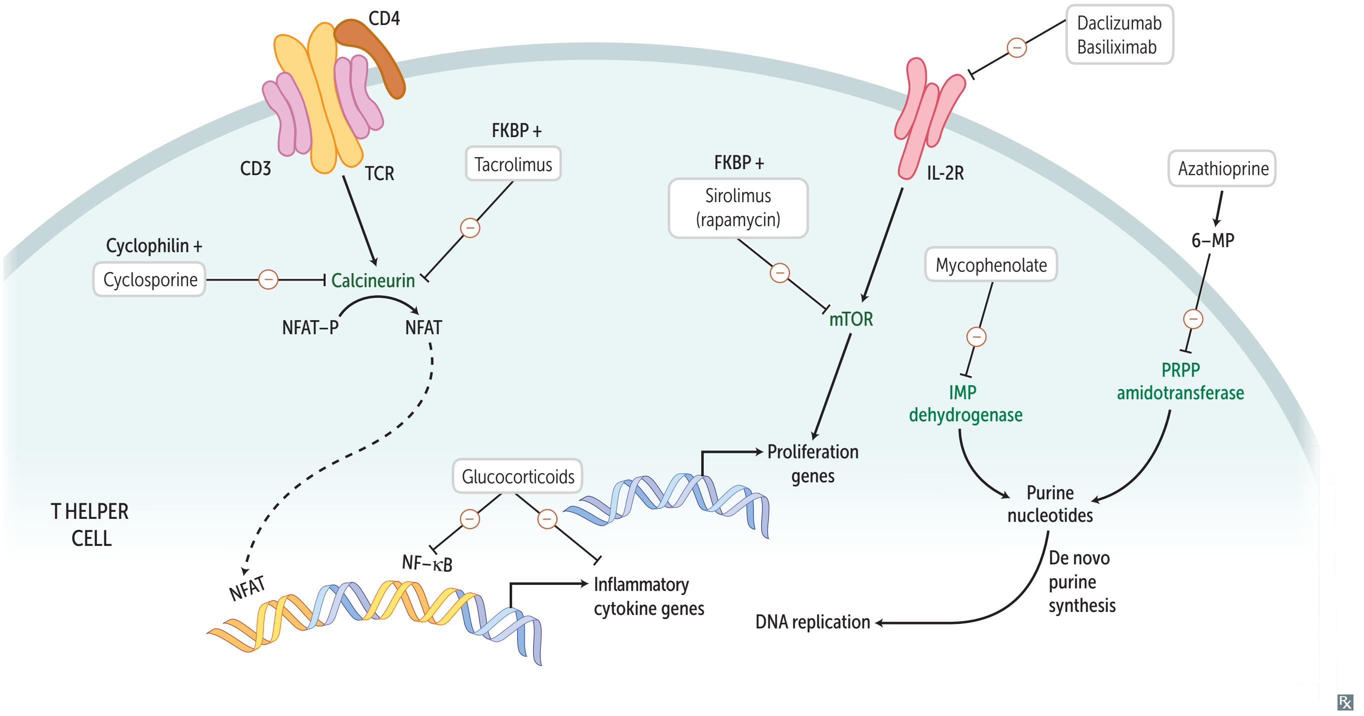
| TYPE OF REJECTION | ONSET | PATHOGENESIS | FEATURES |
|---|---|---|---|
| **Hyperacute**  | Within minutes | Pre-existing recipient antibodies react to donor antigen (type II hypersensitivity reaction), activate complement | Widespread thrombosis of graft vessels (arrows within glomerulus A) → ischemia and fibrinoid necrosis<br>Graft must be removed |
| **Acute**  | Weeks to months | Cellular: CD8+ T cells and/or CD4+ T cells activated against donor MHCs (type IV hypersensitivity reaction)<br>Humoral: similar to hyperacute, except antibodies develop after transplant (associated with C4d deposition) | Vasculitis of graft vessels with dense interstitial lymphocytic infiltrate B<br>Prevent/reverse with immunosuppressants |
| **Chronic**  | Months to years | CD4+ T cells respond to recipient APCs presenting donor peptides, including allogeneic MHC<br>Both cellular and humoral components (type II and IV hypersensitivity reactions) | Recipient T cells react and secrete cytokines → proliferation of vascular smooth muscle, parenchymal atrophy, interstitial fibrosis<br>Dominated by arteriosclerosis C<br>Organ-specific examples:<br>▪ Chronic allograft nephropathy<br>▪ Bronchiolitis obliterans<br>▪ Accelerated atherosclerosis (heart)<br>▪ Vanishing bile duct syndrome |
| **Graft-versus-host disease** | Varies | Grafted immunocompetent T cells proliferate in the immunocompromised host and reject host cells with “foreign” proteins → severe organ dysfunction<br>Type IV hypersensitivity reaction | Maculopapular rash, jaundice, diarrhea, hepatosplenomegaly<br>Usually in bone marrow and liver transplants (rich in lymphocytes)<br>Potentially beneficial in bone marrow transplant for leukemia (graft-versus-tumor effect)<br>For patients who are immunocompromised, irradiate blood products prior to transfusion to prevent GVHD |

## ▶ IMMUNOLOGY—IMMUNOSUPPRESSANTS

**Immunosuppressants** Agents that block lymphocyte activation and proliferation. Reduce acute transplant rejection by suppressing cellular immunity (used as prophylaxis). Frequently combined to achieve greater efficacy with ↓ toxicity. Chronic suppression ↑ risk of infection and malignancy.

| DRUG | MECHANISM | INDICATIONS | TOXICITY | NOTES |
|---|---|---|---|---|
| **Cyclosporine** | Calcineurin inhibitor; binds cyclophilin<br>Blocks T-cell activation by **preventing IL-2 transcription** | Psoriasis, rheumatoid arthritis | **Nephrotoxicity**, hypertension, hyperlipidemia, neurotoxicity, gingival hyperplasia, hirsutism | Both calcineurin inhibitors are highly nephrotoxic, especially in higher doses or in patients with ↓ renal function |
| **Tacrolimus (FK506)** | Calcineurin inhibitor; binds FK506 binding protein (FKBP)<br>Blocks T-cell activation by **preventing IL-2 transcription** | Immunosuppression after solid organ transplant | Similar to cyclosporine, ↑ risk of diabetes and neurotoxicity; no gingival hyperplasia or hirsutism | |
| **Sirolimus (Rapamycin)** | mTOR inhibitor; binds FKBP<br>Blocks T-cell activation and B-cell differentiation by **preventing response to IL-2** | Kidney transplant rejection prophylaxis specifically<br>Sir Basil's kidney transplant | "Pansirtopenia" (pancytopenia), insulin resistance, hyperlipidemia; **not nephrotoxic** | Kidney "sir-vives." Synergistic with cyclosporine<br>Also used in drug-eluting stents |
| **Basiliximab** | Monoclonal antibody; blocks IL-2R | | Edema, hypertension, tremor | |
| **Azathioprine** | Antimetabolite precursor of 6-mercaptopurine<br>Inhibits lymphocyte proliferation by blocking nucleotide synthesis | Rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions | Pancytopenia | 6-MP degraded by xanthine oxidase; toxicity ↑ by allopurinol<br>Pronounce "azathio-purine" |
| **Mycophenolate Mofetil** | Reversibly inhibits IMP dehydrogenase, preventing purine synthesis of B and T cells | Glucocorticoid-sparing agent in rheumatic disease | GI upset, pancytopenia, hypertension, hyperglycemia<br>Less nephrotoxic and neurotoxic | Associated with invasive CMV infection |
| **Glucocorticoids** | Inhibit NF-κB<br>Suppress both B- and T-cell function by ↓ transcription of many cytokines<br>Induce T cell apoptosis | Many autoimmune and inflammatory disorders, adrenal insufficiency, asthma, CLL, non-Hodgkin lymphoma | Cushing syndrome, osteoporosis, hyperglycemia, diabetes, amenorrhea, adrenocortical atrophy, peptic ulcers, psychosis, cataracts, avascular necrosis (femoral head) | Demargination of WBCs causes artificial leukocytosis<br>Adrenal insufficiency may develop if drug is stopped abruptly after chronic use |

### Immunosuppression targets




### Recombinant cytokines and clinical uses

| CYTOKINE | AGENT | CLINICAL USES |
|---|---|---|
| **Bone marrow stimulation** | | |
| Erythropoietin | Epoetin alfa (EPO analog) | Anemias (especially in renal failure)<br>Associated with ↑ risk of hypertension, thromboembolic events |
| Colony stimulating factors | Filgrastim (G-CSF), Sargramostim (GM-CSF) | Leukopenia; recovery of granulocyte and monocyte counts |
| Thrombopoietin | Romiplostim (TPO analog), eltrombopag (think "elthrombopag." TPO receptor agonist) | Autoimmune thrombocytopenia<br>Platelet stimulator |
| **Immunotherapy** | | |
| Toll-like receptor 7 | Imiquimod | Anogenital warts, actinic keratosis |
| Interleukin-2 | Aldesleukin | Renal cell carcinoma, metastatic melanoma |
| Interferons | IFN-α | Chronic hepatitis C (not preferred) and B, renal cell carcinoma |
| | IFN-β | Multiple sclerosis |
| | IFN-γ | Chronic granulomatous disease |

### Therapeutic antibodies

| AGENT | TARGET | CLINICAL USE | NOTES |
|---|---|---|---|
| **Autoimmune disease therapy** | | | |
| **Adalimumab, infliximab** | Soluble TNF-α | IBD, rheumatoid arthritis, ankylosing spondylitis, psoriasis | Screen patients for TB due to risk of reactivation<br>Etanercept is a decoy TNF-α receptor and not a monoclonal antibody |
| **Eculizumab** | Complement protein C5 | Paroxysmal nocturnal hemoglobinuria | |
| **Guselkumab** | IL-23 | Psoriasis | |
| **Ixekizumab, secukinumab** | IL-17A | Psoriasis, psoriatic arthritis | |
| **Natalizumab** | α4-integrin | Multiple sclerosis, Crohn disease | α4-integrin: WBC adhesion<br>Risk of PML in patients with JC virus |
| **Ustekinumab** | IL-12/IL-23 | Psoriasis, psoriatic arthritis | |
| **Vedolizumab** | α4-integrin | IBD | Gut-specific anti-integrin, preventing migration of leukocytes to the gastrointestinal tract |
| **Other applications** | | | |
| **Denosumab** | RANKL | Osteoporosis; inhibits osteoclast maturation (mimics osteoprotegerin) | **Den**osumab helps make **den**se bones |
| **Emicizumab** | Factor IXa and X | Hemophilia A | Bispecific; mimics factor VIII |
| **Omalizumab** | IgE | Refractory allergic asthma; prevents IgE binding to FcεRI | |
| **Palivizumab** | RSV F protein | RSV prophylaxis for high-risk infants | Pali**vi**zumab—**vi**rus |

HIGH-YIELD PRINCIPLES IN

# Microbiology

*"Support bacteria. They're the only culture some people have."*

—Steven Wright

*"What lies behind us and what lies ahead of us are tiny matters compared to what lies within us."*

—Henry S. Haskins

*"Wise and humane management of the patient is the best safeguard against infection."*

—Florence Nightingale

*"I sing and play the guitar, and I'm a walking, talking bacterial infection."*

—Kurt Cobain



Microbiology questions on the Step 1 exam often require two (or more) steps: Given a certain clinical presentation, you will first need to identify the most likely causative organism, and you will then need to provide an answer regarding some features of that organism or relevant antimicrobial agents. For example, a description of a child with fever and a petechial rash will be followed by a question that reads, "From what site does the responsible organism usually enter the blood?"

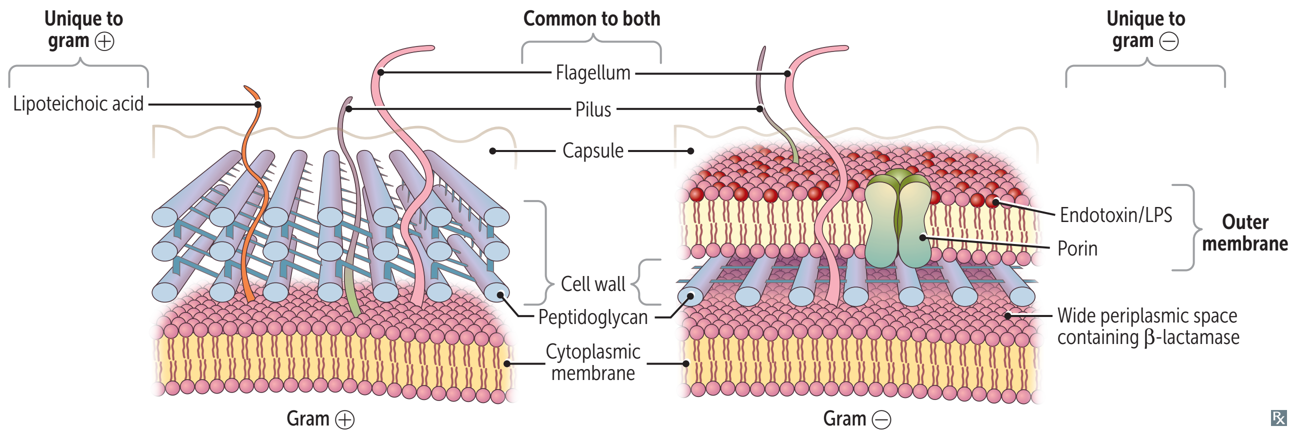
This section therefore presents organisms in two major ways: in individual microbial "profiles" and in the context of the systems they infect and the clinical presentations they produce. You should become familiar with both formats. When reviewing the systems approach, remind yourself of the features of each microbe by returning to the individual profiles. Also be sure to memorize the laboratory characteristics that allow you to identify microbes.

## ▶ MICROBIOLOGY—BASIC BACTERIOLOGY

### Bacterial structures

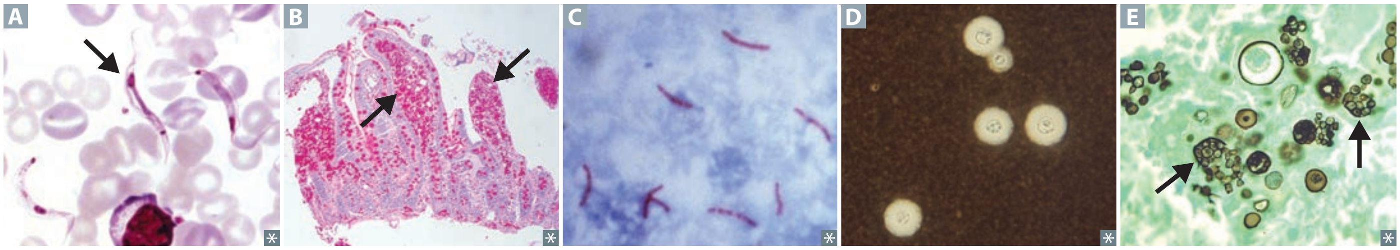
| STRUCTURE | CHEMICAL COMPOSITION | FUNCTION |
|---|---|---|
| **Appendages** | | |
| **Flagellum** | Proteins | Motility |
| **Pilus/fimbria** | Glycoprotein | Mediate adherence of bacteria to cell surface; sex pilus forms during conjugation |
| **Specialized structures** | | |
| **Spore** | Keratin-like coat; dipicolinic acid; peptidoglycan, DNA | Gram ⊕ only<br>Survival: resist dehydration, heat, chemicals |
| **Cell envelope** | | |
| **Capsule** | Discrete layer usually made of polysaccharides (and rarely proteins) | Protects against phagocytosis |
| **Slime (S) layer** | Loose network of polysaccharides | Mediates adherence to surfaces, plays a role in biofilm formation (eg, indwelling catheters) |
| **Outer membrane** | Outer leaflet: contains endotoxin (LPS/LOS)<br>Embedded proteins: porins and other outer membrane proteins (OMPs)<br>Inner leaflet: phospholipids | Gram ⊖ only<br>Endotoxin: lipid A induces TNF and IL-1; antigenic O polysaccharide component<br>Most OMPs are antigenic<br>Porins: transport across outer membrane |
| **Periplasm** | Space between cytoplasmic membrane and outer membrane in gram ⊖ bacteria (peptidoglycan in middle) | Accumulates components exiting gram ⊖ cells, including hydrolytic enzymes (eg, β-lactamases) |
| **Cell wall** | Peptidoglycan is a sugar backbone with peptide side chains cross-linked by transpeptidase | Net-like structure gives rigid support, protects against osmotic pressure damage |
| **Cytoplasmic membrane** | Phospholipid bilayer sac with embedded proteins (eg, penicillin-binding proteins [PBPs]) and other enzymes<br>Li**po**teichoic acids (gram **po**sitive) only extend from membrane to exterior | Site of oxidative and transport enzymes; PBPs involved in cell wall synthesis<br>Lipoteichoic acids induce TNF-α and IL-1 |

### Cell envelope



## Stains

| | | |
|---|---|---|
| **Gram stain** | First-line lab test in bacterial identification. Bacteria with thick peptidoglycan layer retain crystal violet dye (gram ⊕); bacteria with thin peptidoglycan layer turn red or pink (gram ⊖) with counterstain. These bugs do not Gram stain well (**T**hese **L**ittle **M**icrobes **M**ay **U**nfortunately **L**ack **R**eal **C**olor **B**ut **A**re **E**verywhere): | |
| | **T**reponema, ***L**eptospira* | Too thin to be visualized |
| | **M**ycobacteria | Cell wall has high lipid content |
| | ***M**ycoplasma*, ***U**reaplasma* | No cell wall |
| | ***L**egionella*, ***R**ickettsia*, ***C**hlamydia*, ***B**artonella*, ***A**naplasma*, ***E**hrlichia* | Primarily intracellular; also, *Chlamydia* lack classic peptidoglycan because of ↓ muramic acid |
| **Giemsa stain** | *Ch**la**my**dia*, ***Rick**ettsia*, **Tryp**anosomes A, ***Borr**elia*, ***Helico**bacter pylori*, ***Plas**modium* | **Cl**u**msy** **Rick** **Trip**ped on a **Borr**owed **Helico**pter **Plas**tered in **Gems** |
| **Periodic acid–Schiff stain** | Stains **glycogen**, mucopolysaccharides; used to diagnose Whipple disease (*Tropheryma whipplei* B) | **PaS**s the **sugar** |
| **Ziehl-Neelsen stain (carbol fuchsin)** | Acid-fast bacteria (eg, *Mycobacteria* C, *Nocardia*; stains mycolic acid in cell wall); protozoa (eg, *Cryptosporidium* oocysts) | Auramine-rhodamine stain is more often used for screening (inexpensive, more sensitive) |
| **India ink stain** | *Cryptococcus neoformans* D; mucicarmine can also be used to stain thick polysaccharide capsule red | |
| **Silver stain** | Fungi (eg, *Coccidioides* E, *Pneumocystis jirovecii*), *Legionella*, *Helicobacter pylori* | |
| **Fluorescent antibody stain** | Used to identify many bacteria, viruses, *Pneumocystis jirovecii*, *Giardia*, and *Cryptosporidium* | Example is FTA-ABS for syphilis |



| **Properties of growth media** | The same type of media can possess both (or neither) of these properties. |
|---|---|
| **Selective media** | Favors the growth of particular organism while preventing growth of other organisms. Example: Thayer-Martin agar contains antibiotics that allow the selective growth of *Neisseria* by inhibiting the growth of other sensitive organisms. |
| **Indicator (differential) media** | Yields a color change in response to the metabolism of certain organisms. Example: MacConkey agar contains a pH indicator; a lactose fermenter like *E coli* will convert lactose to acidic metabolites → color changes to pink. |

## Special culture requirements

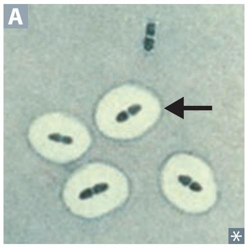
| BUG | MEDIA USED FOR ISOLATION | MEDIA CONTENTS/OTHER |
|---|---|---|
| *H influenzae* | Chocolate agar | Factors V ($NAD^+$) and X (hematin) |
| *N gonorrhoeae, N meningitidis* | Thayer-Martin agar | Selectively favors growth of *Neisseria* by inhibiting growth of gram ⊕ organisms with **v**ancomycin, gram ⊖ organisms except *Neisseria* with **t**rimethoprim and **c**olistin, and fungi with **n**ystatin<br>**V**ery **t**ypically **c**ultures ***N**eisseria* |
| *B pertussis* | Bordet-Gengou agar (**Bordet** for ***Bordet**ella*)<br>Regan-Lowe medium | Potato extract<br>Charcoal, blood, and antibiotic |
| *C diphtheriae* | Tellurite agar, Löffler medium | |
| *M tuberculosis* | Löwenstein-Jensen medium, Middlebrook medium, rapid automated broth cultures | |
| *M pneumoniae* | Eaton agar | Requires cholesterol |
| Lactose-fermenting enterics | MacConkey agar | Fermentation produces acid, causing colonies to turn pink |
| *E coli* | Eosin–methylene blue (EMB) agar | Colonies with green metallic sheen |
| *Brucella, Francisella, Legionella, Pasteurella* | **Charcoal** yeast extract agar buffered with **cysteine** and **iron** | The **Ella** siblings, **Bruce**, **Francis**, a **legion**naire, and a **pasteur** (pastor), built the Sistine (**cysteine**) chapel out of **charcoal** and **iron** |
| Fungi | **Sab**ouraud agar | "**Sab**'s a **fun guy**!" |

| **Aerobes** | Use an $O_2$-dependent system to generate ATP.<br>Examples include *Nocardia*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, and *Bordetella pertussis*.<br>Reactivation of *M tuberculosis* (eg, after immunocompromise or TNF-α inhibitor use) has a predilection for the apices of the lung. |
|---|---|

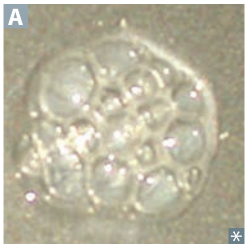
| | | |
|---|---|---|
| **Anaerobes** | Examples include *Clostridium*, *Bacteroides*, *Fusobacterium*, and *Actinomyces israelii*. They lack catalase and/or superoxide dismutase and are thus susceptible to oxidative damage. Generally foul smelling (short-chain fatty acids), are difficult to culture, and produce gas in tissue ($CO_2$ and $H_2$). | Anaerobes Can't Breathe Fresh Air.<br>Anaerobes are normal flora in GI tract, typically pathogenic elsewhere. Amin$O_2$glycosides are ineffective against anaerobes because these antibiotics require $O_2$ to enter into bacterial cell. |
| **Facultative anaerobes** | May use $O_2$ as a terminal electron acceptor to generate ATP, but can also use fermentation and other $O_2$-independent pathways. | Streptococci, staphylococci, and enteric gram ⊖ bacteria. |

**Intracellular bacteria**

| | | |
|---|---|---|
| **Obligate intracellular** | *Rickettsia*, *Chlamydia*, *Coxiella*<br>Rely on host ATP | Stay inside (cells) when it is Really Chilly and Cold |
| **Facultative intracellular** | *Salmonella*, *Neisseria*, *Brucella*, *Mycobacterium*, *Listeria*, *Francisella*, *Legionella*, *Yersinia pestis* | Some Nasty Bugs May Live FacultativeLY |

| | | |
|---|---|---|
| **Encapsulated bacteria**<br> | Examples are *Pseudomonas aeruginosa*, *Streptococcus pneumoniae* A, *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Escherichia coli*, *Salmonella*, *Klebsiella pneumoniae*, and group B Strep. Their capsules serve as an antiphagocytic virulence factor.<br>Capsular polysaccharide + protein conjugate serves as an antigen in vaccines. | Please SHiNE my SKiS.<br>Are opsonized, and then cleared by spleen. Asplenics (No Spleen Here) have ↓ opsonizing ability and thus ↑ risk for severe infections; need vaccines to protect against:<br>▪ *N meningitidis*<br>▪ *S pneumoniae*<br>▪ *H influenzae* |
| **Encapsulated bacteria vaccines** | Some vaccines containing polysaccharide capsule antigens are conjugated to a carrier protein, enhancing immunogenicity by promoting T-cell activation and subsequent class switching. A polysaccharide antigen alone cannot be presented to T cells. | Pneumococcal vaccines: PCV13 (pneumococcal conjugate vaccine), PPSV23 (pneumococcal polysaccharide vaccine with no conjugated protein).<br>*H influenzae* type b (conjugate vaccine).<br>Meningococcal vaccine (conjugate vaccine). |
| **Urease-positive organisms** | *Proteus*, *Cryptococcus*, *H pylori*, *Ureaplasma*, *Nocardia*, *Klebsiella*, *S epidermidis*, *S saprophyticus*. Urease hydrolyzes urea to release ammonia and $CO_2$ → ↑ pH. Predisposes to struvite (magnesium ammonium phosphate) stones, particularly *Proteus*. | Pee CHUNKSS. |

**Catalase-positive organisms**



Catalase degrades $H_2O_2$ into $H_2O$ and bubbles of $O_2$ A before it can be converted to microbicidal products by the enzyme myeloperoxidase. People with chronic granulomatous disease (NADPH oxidase deficiency) have recurrent infections with certain catalase ⊕ organisms.

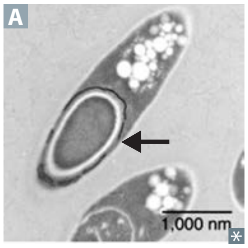
Examples: *Nocardia, Staphylococci, Serratia, Candida, Listeria, E coli, Burkholderia cepacia, Pseudomonas, Aspergillus, Helicobacter pylori, Bordetella pertussis.*

**Pigment-producing bacteria**

| | |
|---|---|
| *Actinomyces* ***israel****ii*—**yellow** "sulfur" **granules**, which are composed of filaments of bacteria | **Israel** has **yellow sand** |
| *S aureus*—**gold**en yellow pigment | ***Aureus*** (Latin) = **gold** |
| *P* ***aerug****inosa*—blue-**green** pigment (pyocyanin and pyoverdin) | **Aerug**ula is **green** |
| ***Serratia*** *marcescens*—**red** pigment | Think **red Sriracha** hot sauce |

**In vivo biofilm-producing bacteria**

| | |
|---|---|
| *S epidermidis* | Catheter and prosthetic device infections |
| Viridans streptococci (*S mutans, S sanguinis*) | Dental plaques, infective endocarditis |
| *P aeruginosa* | Respiratory tree colonization in patients with cystic fibrosis, ventilator-associated pneumonia<br>Contact lens–associated keratitis |
| Nontypeable (unencapsulated) *H influenzae* | Otitis media |

| | | |
|---|---|---|
| **Spore-forming bacteria**<br>A  | Some gram ⊕ bacteria can form spores A when nutrients are limited. Spores lack metabolic activity and are highly resistant to heat and chemicals. Core contains dipicolinic acid (responsible for heat resistance). Must autoclave to kill spores (as is done to surgical equipment) by steaming at 121°C for 15 minutes. Hydrogen peroxide and iodine-based agents are also sporicidal. | Examples: B *anthracis* (anthrax), B *cereus* (food poisoning), C *botulinum* (botulism), C *difficile* (pseudomembranous colitis), C *perfringens* (gas gangrene), C *tetani* (tetanus). |

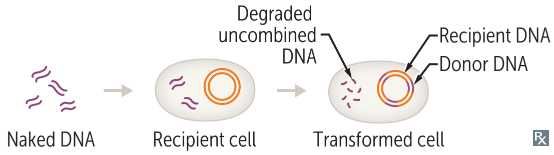
| | |
|---|---|
| **Bacterial virulence factors** | These promote evasion of host immune response. |
| **Protein A** | Binds Fc region of IgG. Prevents opsonization and phagocytosis. Expressed by S *aureus*. |
| **IgA protease** | Enzyme that cleaves IgA, allowing bacteria to adhere to and colonize mucous membranes. Secreted by **S** *pneumoniae*, **H** *influenzae* type b, and **N***eisseria* (**SHiN**). |
| **M protein** | Helps prevent phagocytosis. Expressed by group A streptococci. Sequence homology with human tropomyosin and myosin (**m**olecular **m**imicry); possibly underlies the autoimmune response seen in acute rheumatic fever. |

## Bacterial genetics

### Transformation

Competent bacteria can bind and import short pieces of environmental naked bacterial chromosomal DNA (from bacterial cell lysis). The transfer and expression of newly transferred genes is called transformation. A feature of many bacteria, especially ***S** pneumoniae*, ***H** influenzae* type b, and ***N**eisseria* (**SHiN**).

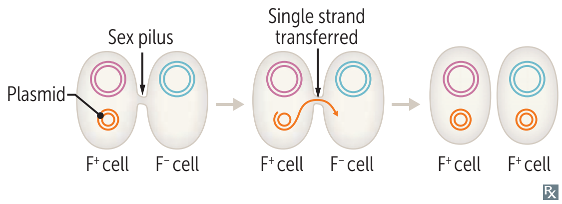
Adding deoxyribonuclease degrades naked DNA, preventing transformation.




### Conjugation

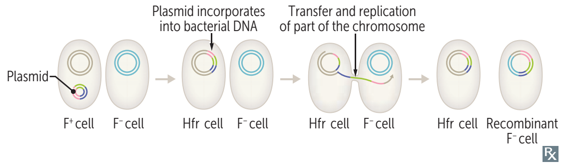
#### $F^+ \times F^-$

$F^+$ plasmid contains genes required for sex pilus and conjugation. Bacteria without this plasmid are termed $F^-$. Sex pilus on $F^+$ bacterium contacts $F^-$ bacterium. A single strand of plasmid DNA is transferred across the conjugal bridge ("mating bridge"). No transfer of chromosomal DNA.




#### $Hfr \times F^-$

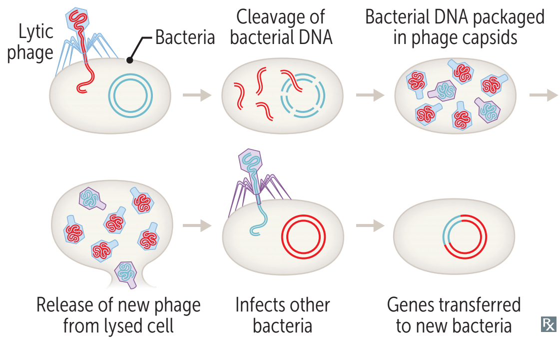
$F^+$ plasmid can become incorporated into bacterial chromosomal DNA, termed high-frequency recombination (Hfr) cell. Transfer of leading part of plasmid and a few flanking chromosomal genes. High-frequency recombination may integrate some of those bacterial genes. Recipient cell remains $F^-$ but now may have new bacterial genes.




### Transduction

#### Generalized

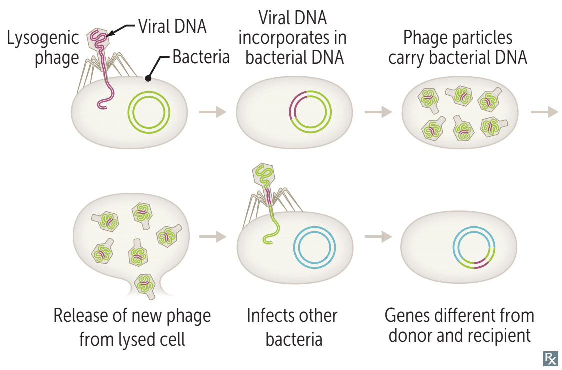
A "packaging" error. Lytic phage infects bacterium, leading to cleavage of bacterial DNA. Parts of bacterial chromosomal DNA may become packaged in phage capsid. Phage infects another bacterium, transferring these genes.




#### Specialized

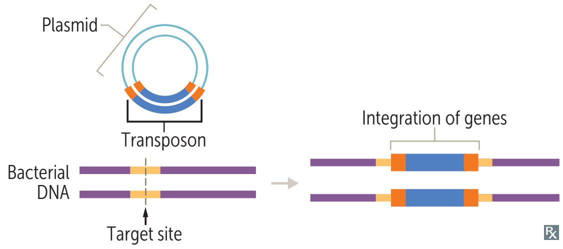
An "excision" event. Lysogenic phage infects bacterium; viral DNA incorporates into bacterial chromosome. When phage DNA is excised, flanking bacterial genes may be excised with it. DNA is packaged into phage capsid and can infect another bacterium.

Genes for the following 5 bacterial toxins are encoded in a lysogenic phage (**ABCD'S**): Group **A** strep erythrogenic toxin, **B**otulinum toxin, **C**holera toxin, **D**iphtheria toxin, **S**higa toxin.



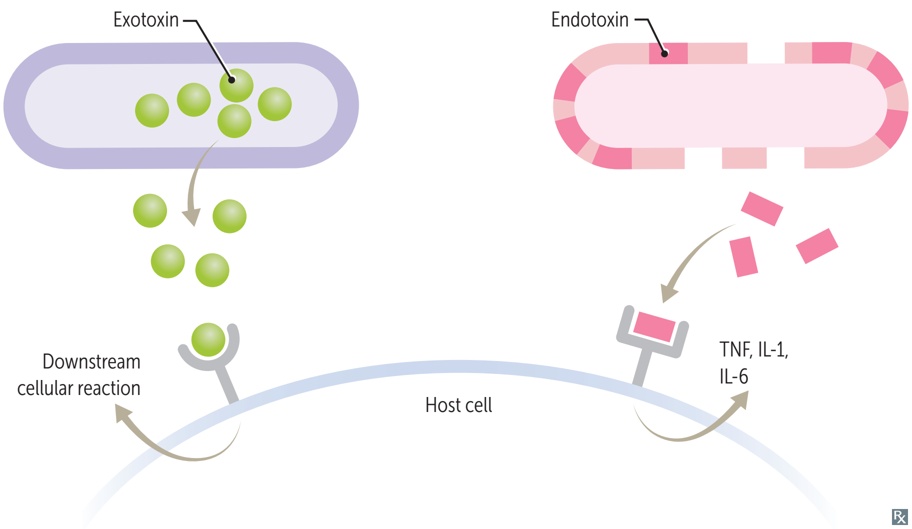
## Bacterial genetics *(continued)*

| | |
|---|---|
| **Transposition** | A "jumping" process involving a transposon (specialized segment of DNA), which can copy and excise itself and then insert into the same DNA molecule or an unrelated DNA (eg, plasmid or chromosome). Critical in creating plasmids with multiple drug resistance and transfer across species lines (eg, Tn*1546* with *van*A from *Enterococcus* to *S aureus*). |




## Main features of exotoxins and endotoxins

| | Exotoxins | Endotoxins |
|---|---|---|
| SOURCE | Certain species of gram ⊕ and gram ⊖ bacteria | Outer cell membrane of most gram ⊖ bacteria |
| SECRETED FROM CELL | Yes | No |
| CHEMISTRY | Polypeptide | Lipid A component of LPS (structural part of bacteria; released when lysed) |
| LOCATION OF GENES | Plasmid or bacteriophage | Bacterial chromosome |
| TOXICITY | High (fatal dose on the order of 1 µg) | Low (fatal dose on the order of hundreds of micrograms) |
| CLINICAL EFFECTS | Various effects (see following pages) | Fever, shock (hypotension), DIC |
| MODE OF ACTION | Various modes (see following pages) | Induces TNF, IL-1, and IL-6 |
| ANTIGENICITY | Induces high-titer antibodies called antitoxins | Poorly antigenic |
| VACCINES | Toxoids used as vaccines | No toxoids formed and no vaccine available |
| HEAT STABILITY | Destroyed rapidly at 60°C (except staphylococcal enterotoxin and *E coli* heat-stable toxin) | Stable at 100°C for 1 hr |
| TYPICAL DISEASES | Tetanus, botulism, diphtheria, cholera | Meningococcemia; sepsis by gram ⊖ rods |



### Bacteria with exotoxins

| BACTERIA | TOXIN | MECHANISM | MANIFESTATION |
|---|---|---|---|
| **Inhibit protein synthesis** | | | |
| ***Corynebacterium diphtheriae*** | Diphtheria toxin[a] | Inactivate elongation factor (EF-2) | Pharyngitis with pseudomembranes in throat and severe lymphadenopathy (bull neck), myocarditis |
| ***Pseudomonas aeruginosa*** | Exotoxin A[a] | | Host cell death |
| ***Shigella* spp**<br>**Enterohemorrhagic *E coli*** | Shiga toxin[a] | Inactivate 60S ribosome by removing adenine from rRNA | Damages GI mucosa → dysentery<br>Enhances cytokine release → hemolytic-uremic syndrome (HUS; prototypically in EHEC serotype O157:H7)<br>Unlike *Shigella*, EHEC does not invade host cells |
| **Increase fluid secretion** | | | |
| **Enterotoxigenic *E coli*** | Heat-**labile** toxin (LT)[a] | Overactivates adenylate cyclase (↑ cAMP) → ↑ $Cl^-$ secretion in gut and $H_2O$ efflux | Watery diarrhea: "**labile** in the **A**ir (**A**denylate cyclase), **stable** on the **G**round (**G**uanylate cyclase)"<br>Bacteria that **↑ cAMP** include **C**holera, **A**nthracis, **P**ertussis, ***E** coli*; "**Increase cAMP** with **CAPE**" |
| | Heat-**stable** toxin (ST) | Overactivates guanylate cyclase (↑ c**G**MP) → ↓ resorption of NaCl and $H_2O$ in gut | |
| ***Bacillus anthracis*** | Anthrax toxin[a] | Mimics adenylate cyclase (↑ cAMP) | Likely responsible for characteristic edematous borders of black eschar in cutaneous anthrax |
| ***Vibrio cholerae*** | Cholera toxin[a] | Overactivates adenylate cyclase (↑ cAMP) by permanently activating $G_s$ | Voluminous "rice-water" diarrhea |
| **Inhibit phagocytic ability** | | | |
| ***Bordetella pertussis*** | Pertussis toxin[a] | Inactivates inhibitory G subunit ($G_i$) → activation of adenylate cyclase → ↑ cAMP | Whooping cough—child coughs on expiration and "whoops" on inspiration; can cause "100-day cough" in adults; associated with posttussive emesis |
| **Inhibit release of neurotransmitter** | | | |
| ***Clostridium tetani*** | Tetanospasmin[a] | Both are proteases that cleave SNARE (soluble NSF attachment protein receptor), a set of proteins required for neurotransmitter release via vesicular fusion | Toxin prevents release of **inhibitory** (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord → spastic paralysis, risus sardonicus, trismus (lockjaw), opisthotonos |
| ***Clostridium botulinum*** | Botulinum toxin[a] | | Infant botulism—caused by ingestion of spores (eg, from soil, raw honey). Toxin produced in vivo<br>Foodborne botulism—caused by ingestion of preformed toxin (eg, from canned foods) |

[a]An AB toxin (aka, two-component toxin [or three for anthrax]) with **B** enabling **B**inding and triggering uptake (endocytosis) of the **A**ctive **A** component. The A components are usually ADP ribosyltransferases; others have enzymatic activities as listed in chart.

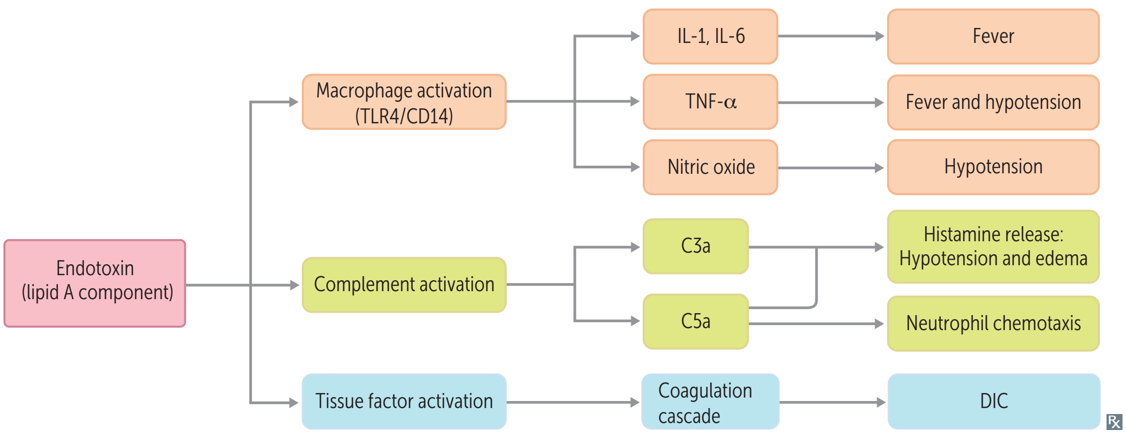
### Bacteria with exotoxins *(continued)*

| BACTERIA | TOXIN | MECHANISM | MANIFESTATION |
|---|---|---|---|
| **Lyse cell membranes** | | | |
| ***Clostridium perfringens*** | Alpha toxin | Phospholipase (lecithinase) that degrades tissue and cell membranes | Degradation of phospholipids → myonecrosis ("gas gangrene") and hemolysis ("double zone" of hemolysis on blood agar) |
| ***Streptococcus pyogenes*** | Streptolysin O | Protein that degrades cell membrane | Lyses RBCs; contributes to β-hemolysis; host antibodies against toxin (ASO) used to diagnose rheumatic fever (do not confuse with immune complexes of poststreptococcal glomerulonephritis) |
| **Superantigens causing shock** | | | |
| ***Staphylococcus aureus*** | Toxic shock syndrome toxin (TSST-1) | Cross-links β region of TCR to MHC class II on APCs outside of the antigen binding site → overwhelming release of IL-1, IL-2, IFN-γ, and TNF-α → shock | Toxic shock syndrome: fever, rash, shock; other toxins cause scalded skin syndrome (exfoliative toxin) and food poisoning (heat-stable enterotoxin) |
| ***Streptococcus pyogenes*** | Erythrogenic exotoxin A | | Toxic shock–like syndrome: fever, rash, shock; scarlet fever |

## Endotoxin

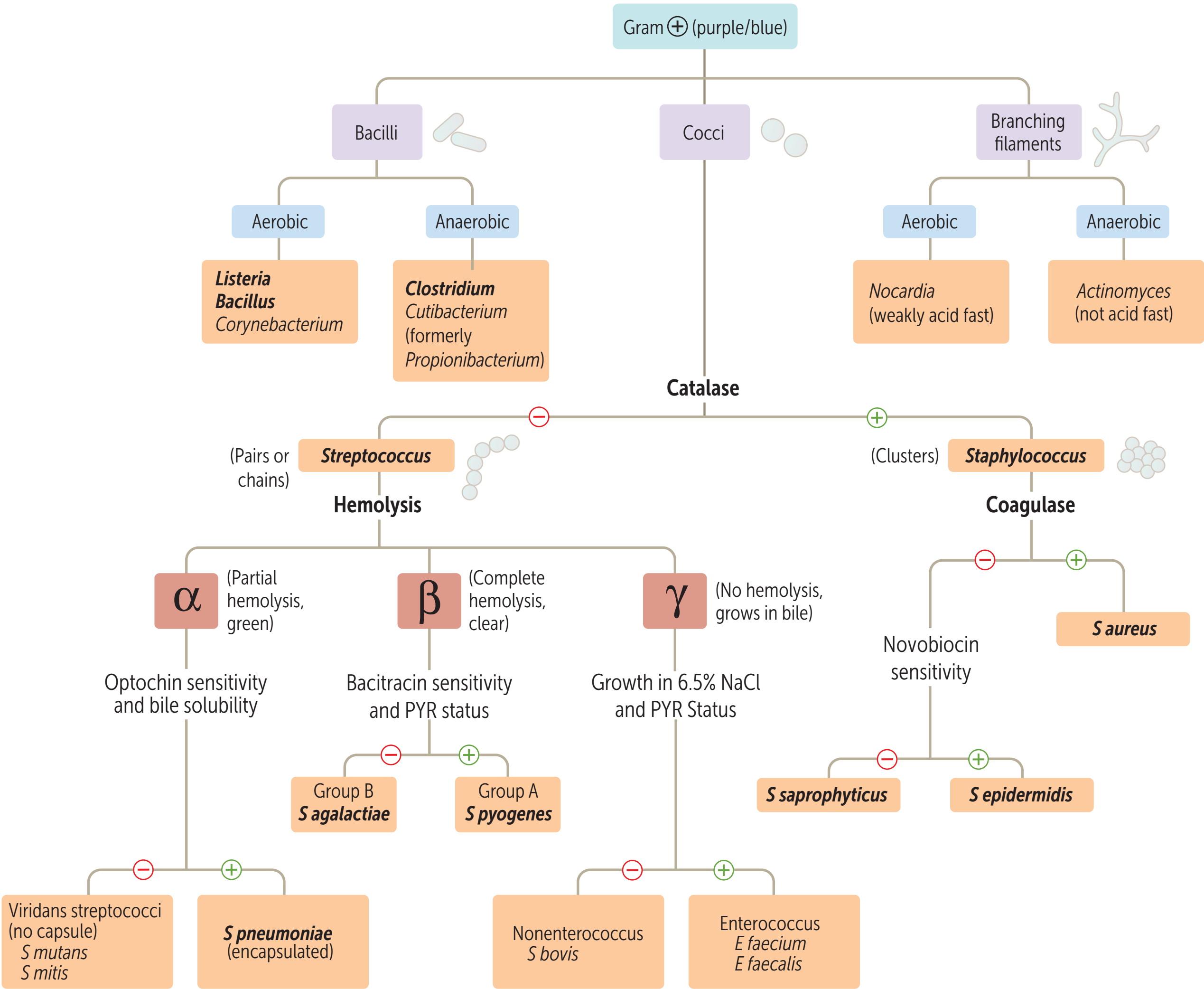
LPS found in outer membrane of gram ⊖ bacteria (both cocci and rods). Composed of O-antigen + core polysaccharide + lipid A (the toxic component).
Released upon cell lysis or by living cells by blebs detaching from outer surface membrane (vs exotoxin, which is actively secreted).
Three main effects: macrophage activation (TLR4/CD14), complement activation, and tissue factor activation.

**ENDOTOXINS**:
- **E**dema
- **N**itric oxide
- **D**IC/**D**eath
- **O**uter membrane
- **T**NF-α
- **O**-antigen + core polysaccharide + lipid A
- e**X**tremely heat stable
- **I**L-1 and **I**L-6
- **N**eutrophil chemotaxis
- **S**hock



## ▶ MICROBIOLOGY—CLINICAL BACTERIOLOGY

### Gram-positive lab algorithm

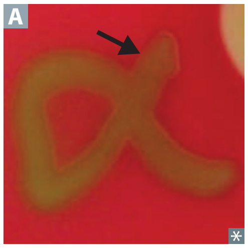



Important **tests** are in **bold.** Important ***pathogens*** are in ***bold italics.***
Note: Enterococcus is either α- or γ-hemolytic.

### Gram-positive cocci antibiotic tests

| | | |
|---|---|---|
| **Staphylococci** | Novobiocin—Saprophyticus is resistant; epidermidis is sensitive | Sapro is a no-go on Novo |
| **Streptococci** | Optochin—*Viridans* is Resistant; *Pneumoniae* is Sensitive | OVRPS (overpass) |
| | Bacitracin—group B strep are Resistant; group A strep are Sensitive | B-BRAS |

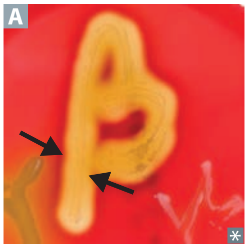
### α-hemolytic bacteria



Gram ⊕ cocci. Partial oxidation of hemoglobin causes greenish or brownish color without clearing around growth on blood agar A. Include the following organisms:

- *Streptococcus pneumoniae* (catalase ⊖ and optochin sensitive)
- Viridans streptococci (catalase ⊖ and optochin resistant)

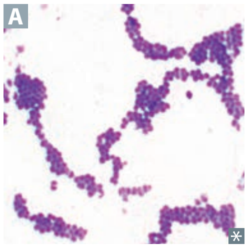
### β-hemolytic bacteria



Gram ⊕ cocci. Complete lysis of RBCs → pale/clear area surrounding colony on blood agar A. Include the following organisms:

- *Staphylococcus aureus* (catalase and coagulase ⊕)
- *Streptococcus pyogenes*—group A strep (catalase ⊖ and bacitracin sensitive)
- *Streptococcus agalactiae*—group B strep (catalase ⊖ and bacitracin resistant)

### *Staphylococcus aureus*



Gram ⊕, β-hemolytic, catalase ⊕, coagulase ⊕ cocci in clusters A. Protein A (virulence factor) binds Fc-IgG, inhibiting complement activation and phagocytosis. Commonly colonizes the nares, ears, axilla, and groin.

Causes:

- Inflammatory disease—skin infections, organ abscesses, pneumonia (often after influenza virus infection), endocarditis, septic arthritis, and osteomyelitis.
- Toxin-mediated disease—toxic shock syndrome (TSST-1), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins).

MRSA (methicillin-resistant *S aureus*)—important cause of serious nosocomial and community-acquired infections. Resistance due to altered penicillin-binding proteins (conferred by *mec*A gene). Some strains release Panton-Valentine leukocidin (PVL), which kills leukocytes and causes tissue necrosis.

TSST-1 is a superantigen that binds to MHC II and T-cell receptor, resulting in polyclonal T-cell activation and cytokine release.

Staphylococcal toxic shock syndrome (TSS)—fever, vomiting, diarrhea, rash, desquamation, shock, end-organ failure. TSS results in ↑ AST, ↑ ALT, ↑ bilirubin. Associated with prolonged use of vaginal tampons or nasal packing.

Compare with *Streptococcus pyogenes* TSS (a toxic shock–like syndrome associated with painful skin infection).

*S aureus* food poisoning due to ingestion of preformed toxin → short incubation period (2–6 hr) followed by nonbloody diarrhea and emesis. Enterotoxin is heat stable → not destroyed by cooking.

*S aureus* makes coagulase and toxins. Forms fibrin clot around itself → abscess.

### *Staphylococcus epidermidis*

Gram ⊕, catalase ⊕, coagulase ⊖, urease ⊕ cocci in clusters. Novobiocin sensitive. Does not ferment mannitol (vs *S aureus*).

Normal flora of skin; contaminates blood cultures.

Infects prosthetic devices (eg, hip implant, heart valve) and IV catheters by producing adherent biofilms.

### ***Staphylococcus saprophyticus***

Gram ⊕, catalase ⊕, coagulase ⊖, urease ⊕ cocci in clusters. Novobiocin resistant.
Normal flora of female genital tract and perineum.
Second most common cause of uncomplicated UTI in young females (most common is *E coli*).

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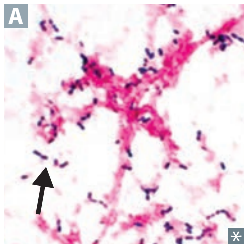
### ***Streptococcus pneumoniae***

A



Gram ⊕, α-hemolytic, lancet-shaped diplococci A.
Encapsulated. IgA protease. Optochin sensitive and bile soluble.
Most commonly causes **MOPS**:
- **M**eningitis
- **O**titis media (in children)
- **P**neumonia
- **S**inusitis

Pneumococcus is associated with "rusty" sputum, patients with hyposplenia or asplenia.
No virulence without capsule.

---

### **Viridans group streptococci**

Gram ⊕, α-hemolytic cocci. Optochin resistant and bile insoluble. Normal flora of the oropharynx.
*Streptococcus mutans* and *S mitis* cause dental caries.
*S sanguinis* makes dextrans that bind to fibrin-platelet aggregates on damaged **heart** valves, causing subacute bacterial endocarditis.

Viridans group strep live in the mouth, because they are not afraid **of-the-chin** (**op-to-chin** resistant).
*Sanguinis* = **blood**. Think, "there is lots of **blood** in the **heart**" (endocarditis).

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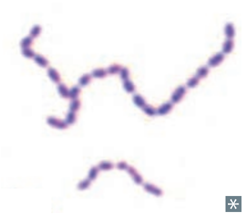
### ***Streptococcus pyogenes* (group A streptococci)**

A



Gram ⊕ cocci in chains A. Group A strep cause:
- Pyogenic—pharyngitis, cellulitis, impetigo ("honey-crusted" lesions), erysipelas
- Toxigenic—scarlet fever, toxic shock–like syndrome, necrotizing fasciitis
- Immunologic—rheumatic fever, glomerulonephritis

Bacitracin sensitive, β-hemolytic, pyrrolidonyl arylamidase (PYR) ⊕. Hyaluronic acid capsule and M protein inhibit phagocytosis. Antibodies to M protein enhance host defenses against *S pyogenes* but can give rise to rheumatic fever.
Diagnose strep pharyngitis via throat swab, which can be tested with an antigen detection assay (rapid, in-office results) or cultured on blood agar (results in 48 hours).

"**Ph**"yogenes **ph**aryngitis can result in rheumatic "**ph**ever" and glomerulone**ph**ritis.
Strains causing impetigo can induce glomerulonephritis.
Key virulence factors include DNase, erythrogenic exotoxin, streptokinase, streptolysin O. ASO titer or anti-DNase B antibodies indicate recent *S pyogenes* infection.
Scarlet fever—blanching, sandpaper-like body rash, strawberry tongue, and circumoral pallor in the setting of group A streptococcal pharyngitis (erythrogenic toxin ⊕).

| | | |
|---|---|---|
| ***Streptococcus agalactiae* (group B streptococci)** | Gram ⊕ cocci, bacitracin resistant, β-hemolytic, colonizes vagina; causes pneumonia, meningitis, and sepsis, mainly in babies. Polysaccharide capsule confers virulence.<br>Produces CAMP factor, which enlarges the area of hemolysis formed by *S aureus*. (Note: CAMP stands for the authors of the test, not cyclic AMP.) Hippurate test ⊕. PYR ⊖.<br>Screen pregnant patients at 35–37 weeks' gestation with rectal and vaginal swabs. Patients with ⊕ culture receive intrapartum penicillin/ampicillin prophylaxis. | Group B for Babies! |
| ***Streptococcus bovis*** | Gram ⊕ cocci, colonizes the gut. *S gallolyticus* (*S bovis* biotype 1) can cause bacteremia and subacute endocarditis. Patients with *S bovis* endocarditis have ↑ incidence of colon cancer. | Bovis in the blood = cancer in the colon. |
| **Enterococci** | Gram ⊕ cocci. Enterococci (*E faecalis* and *E faecium*) are normal colonic flora that are penicillin G resistant and cause UTI, biliary tract infections, and subacute endocarditis (following GI/GU procedures). Catalase ⊖, PYR ⊕, typically nonhemolytic.<br>VRE (vancomycin-resistant enterococci) are an important cause of nosocomial infection. | Enterococci are more resilient than streptococci, can grow in 6.5% NaCl and bile (lab test).<br>*Entero* = intestine, *faecalis* = feces, *strepto* = twisted (chains), *coccus* = berry. |
| ***Bacillus anthracis*** | Gram ⊕, spore-forming rod that produces anthrax toxin (an exotoxin consisting of protective antigen, lethal factor, and edema factor). Has a polypeptide capsule (poly D-glutamate). Colonies show a halo of projections, sometimes referred to as "medusa head" appearance. | |
| **Cutaneous anthrax**  | Painless papule surrounded by vesicles → ulcer with black eschar A (painless, necrotic) → uncommonly progresses to bacteremia and death. | |
| **Pulmonary anthrax** | Inhalation of spores, most commonly from contaminated animals or animal products, although also a potential bioweapon → flu-like symptoms that rapidly progress to fever, pulmonary hemorrhage, mediastinitis (CXR may show widened mediastinum), and shock. Also called woolsorter's disease. Prophylaxis with ciprofloxacin or doxycycline when exposed. | |

### *Bacillus cereus*

Gram ⊕ rod. Causes food poisoning. Spores survive cooking rice (reheated rice syndrome). Keeping rice warm results in germination of spores and enterotoxin formation.
Emetic type causes nausea and vomiting within 1–5 hours. Caused by cereulide, a preformed toxin.
Diarrheal type causes watery, nonbloody diarrhea and GI pain within 8–18 hours.
Management: supportive care (antibiotics are ineffective against toxins).

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### Clostridia

Gram ⊕, spore-forming, obligate anaerobic rods. Tetanus toxin and botulinum toxin are proteases that cleave SNARE proteins involved in neurotransmission.

#### *Clostridium tetani*

Pathogen is noninvasive and remains localized to wound site. Produces tetanospasmin, an exotoxin causing tetanus. Tetano**spas**min spreads by retrograde axonal transport to CNS and blocks release of GABA and glycine from Renshaw cells in spinal cord.
Causes **spas**tic paralysis, trismus (lockjaw), risus sardonicus (raised eyebrows and open grin), opisthotonos (spasms of spinal extensors).

**Tet**anus is **tet**anic paralysis.
Prevent with tetanus vaccine. Treat with antitoxin +/– vaccine booster, antibiotics, diazepam (for muscle spasms), and wound debridement.

#### *Clostridium botulinum*

Produces a heat-labile toxin that inhibits ACh release at the neuromuscular junction, causing botulism. In babies, ingestion of spores (eg, in honey) leads to disease (**floppy** baby syndrome). In adults, disease is caused by ingestion of preformed toxin (eg, in canned food).
Symptoms of botulism (the **5 D**'s): **d**iplopia, **d**ysarthria, **d**ysphagia, **d**yspnea, **d**escending **flaccid** paralysis. Does not present with sensory deficits.

***Bot**ulinum* is from bad **bot**tles of food, juice, and honey.
Treatment: human botulinum immunoglobulin.
Local botulinum toxin A (Botox) injections used to treat focal dystonia, hyperhidrosis, muscle spasms, and cosmetic reduction of facial wrinkles.

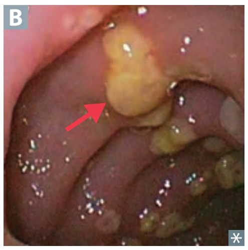
#### *Clostridium perfringens*

A


Produces α-toxin (lecithinase, a phospholipase) that can cause myonecrosis (gas gangrene A; presents as soft tissue crepitus) and hemolysis.
If heavily spore-contaminated food is cooked but left standing too long at < 60°C, spores germinate → vegetative bacteria → heat-labile enterotoxin → late-onset (10-12 hours) food poisoning symptoms, resolution in 24 hours.

***Perf**ringens* **perf**orates a gangrenous leg.

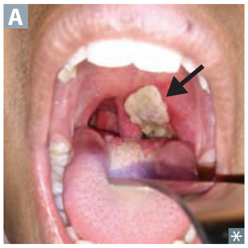
#### *Clostridioides difficile*

B


Produces toxins A and B, which damage enterocytes. Both toxins lead to watery diarrhea → pseudomembranous colitis B. Often 2° to antibiotic use, especially clindamycin, ampicillin, cephalosporins, fluoroquinolones; associated with PPIs.
Fulminant infection: toxic megacolon, ileus, shock.

***Di**fficile* causes **di**arrhea.
Diagnosed by PCR or antigen detection of one or both toxins in stool.
Treatment: oral vancomycin or fidaxomicin. For recurrent cases, consider repeating prior regimen or fecal microbiota transplant.

### *Corynebacterium diphtheriae*



Gram ⊕ rods occurring in angular arrangements; transmitted via respiratory droplets. Causes diphtheria via exotoxin encoded by β-prophage. Potent exotoxin inhibits protein synthesis via ADP-ribosylation of EF-2, leading to possible necrosis in pharynx, cardiac, and CNS tissue.

Symptoms include pseudomembranous pharyngitis (grayish-white membrane A) with lymphadenopathy ("bull's neck" appearance). Toxin dissemination may cause myocarditis, arrhythmias, neuropathies.

Lab diagnosis based on gram ⊕ rods with metachromatic (blue and red) granules and ⊕ Elek test for toxin.

Toxoid vaccine prevents diphtheria.

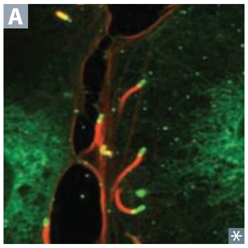
*Coryne* = club shaped (metachromatic granules on Löffler media).

Black colonies on cystine-tellurite agar.

**ABCDEFG**:
- **A**DP-ribosylation
- **β**-prophage
- ***C****orynebacterium*
- ***D****iphtheriae*
- **E**longation **F**actor 2
- **G**ranules

Treatment: diphtheria antitoxin +/– erythromycin or penicillin.

### *Listeria monocytogenes*



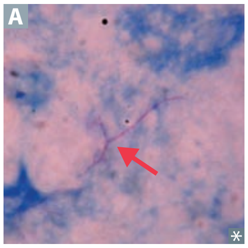
Gram ⊕, facultative intracellular rod; acquired by ingestion of unpasteurized dairy products and cold deli meats, transplacental transmission, by vaginal transmission during birth. Grows well at refrigeration temperatures ("cold enrichment").

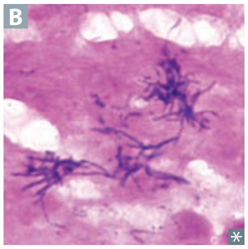
Forms "rocket tails" (red in A) via actin polymerization that allow intracellular movement and cell-to-cell spread across cell membranes, thereby avoiding antibody. Characteristic tumbling motility in broth.

Can cause amnionitis, septicemia, and spontaneous abortion in pregnant patients; granulomatosis infantiseptica; meningitis in immunocompromised patients, neonates, and older adults; mild, self-limited gastroenteritis in healthy individuals.

Treatment: ampicillin.

### *Nocardia* vs *Actinomyces*



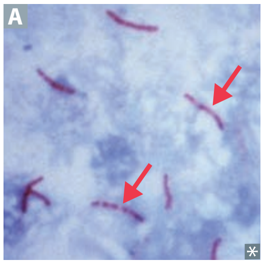


Both are gram ⊕ and form long, branching filaments resembling fungi.

| *Nocardia* | *Actinomyces* |
|---|---|
| Aerobe | Anaerobe |
| Acid fast (weak) A | Not acid fast B |
| Found in soil | Normal oral, reproductive, and GI flora |
| Causes pulmonary infections in immunocompromised (can mimic TB but with ⊖ PPD); cutaneous infections after trauma in immunocompetent; can spread to CNS → cerebral abscess | Causes oral/facial abscesses that drain through sinus tracts; often associated with dental caries/extraction and other maxillofacial trauma; forms yellow "sulfur granules"; can also cause PID with IUDs |
| Treat with sulfonamides (TMP-SMX) | Treat with penicillin |

Treatment is a **SNAP**: **S**ulfonamides—***N****ocardia*; ***A****ctinomyces*—**P**enicillin

## Mycobacteria




Acid-fast rods (pink rods, arrows in A).

*Mycobacterium tuberculosis* (TB, often resistant to multiple drugs).

*M avium–intracellulare* (causes disseminated, non-TB disease in AIDS; often resistant to multiple drugs). Prophylaxis with azithromycin when CD4+ count < 50 cells/mm$^3$.

*M scrofulaceum* (cervical lymphadenitis in children).

*M marinum* (hand infection in aquarium handlers).

TB symptoms include fever, night sweats, weight loss, cough (nonproductive or productive), hemoptysis.

Cord factor creates a "serpentine cord" appearance in virulent *M tuberculosis* strains; activates macrophages (promoting granuloma formation) and induces release of TNF-α. Sulfatides (surface glycolipids) inhibit phagolysosomal fusion.

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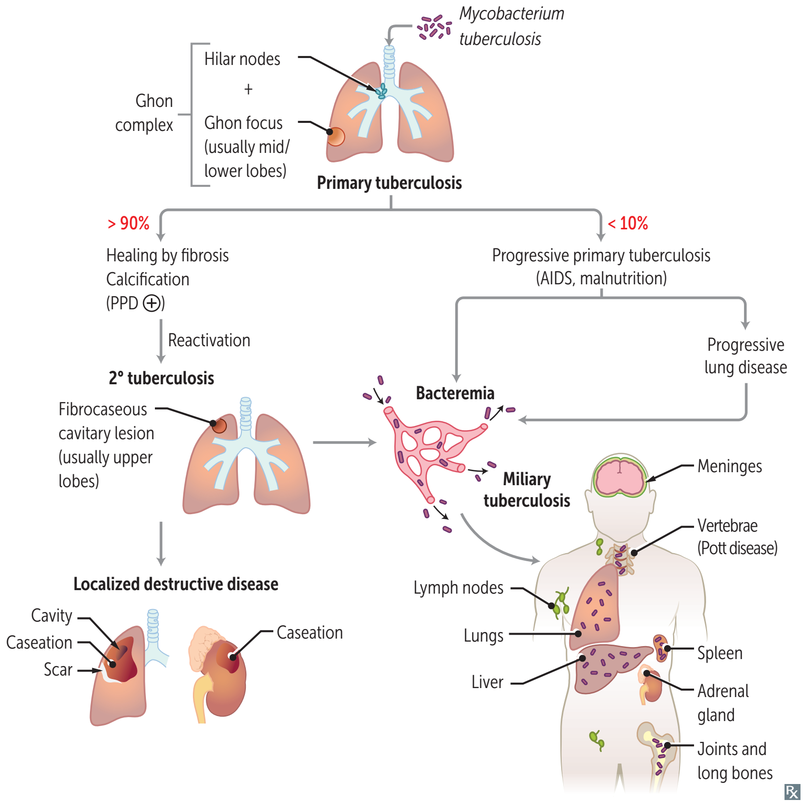
## Tuberculosis



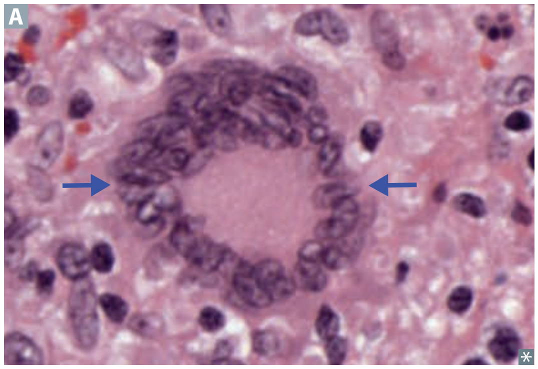

PPD ⊕ if current infection or past exposure.

PPD ⊖ if no infection and in immunocompromised patients (especially with low CD4+ cell count).

Interferon-γ release assay (IGRA) has fewer false positives from BCG vaccination.

Caseating granulomas with central necrosis and Langhans giant cell (single example in A) are characteristic of 2° tuberculosis. Do not confuse Langhans giant cell with Langerhans cell, an APC.

TB reactivation risk highest in immunocompromised individuals (eg, HIV, organ transplant recipients).



### Leprosy



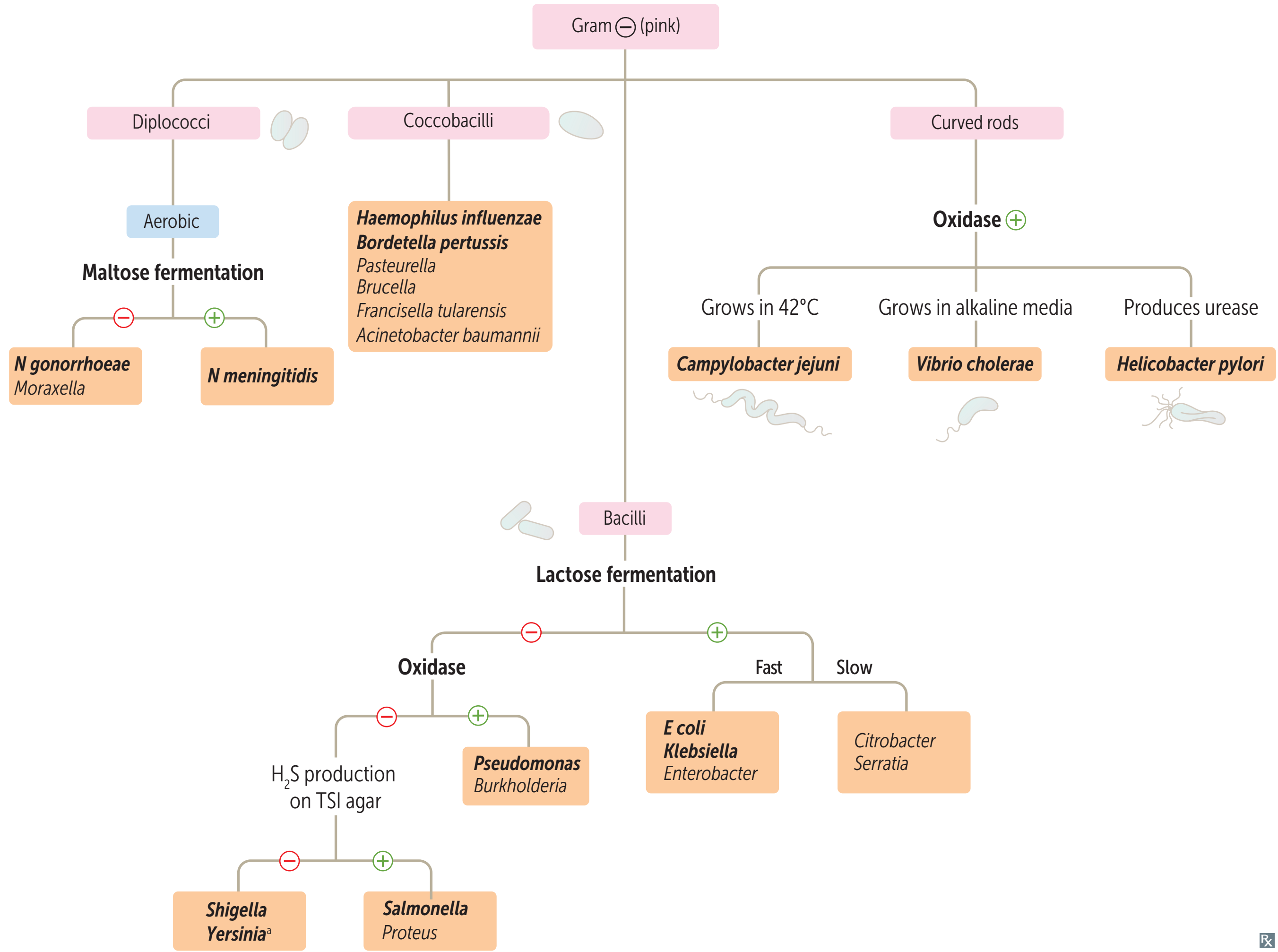
Also called Hansen disease. Caused by *Mycobacterium leprae*, an acid-fast bacillus that likes cool temperatures (infects skin and superficial nerves—"glove and stocking" loss of sensation A) and cannot be grown in vitro. Diagnosed via skin biopsy or tissue PCR. Reservoir in United States: armadillos.

Leprosy has 2 forms (many cases fall temporarily between two extremes):

- Lepromatous—presents diffusely over the skin, with leonine (lion-like) facies B, and is communicable (high bacterial load); characterized by low cell-mediated immunity with a largely Th2 response. Lepromatous form can be lethal.
- Tuberculoid—limited to a few hypoesthetic, hairless skin plaques; characterized by high cell-mediated immunity with a largely Th1-type response and low bacterial load.

Treatment: dapsone and rifampin for tuberculoid form; clofazimine is added for lepromatous form.

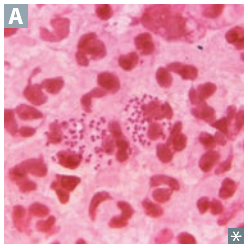
### Gram-negative lab algorithm




Important **tests** are in **bold.** Important ***pathogens*** are in ***bold italics.***

[a]Pleomorphic rod/coccobacillus

## Neisseria





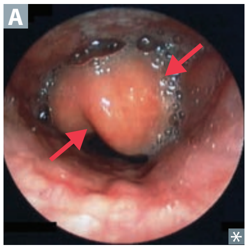
Gram ⊖ diplococci. Metabolize glucose and produce IgA proteases. Contain lipooligosaccharides (LOS) with strong endotoxin activity.

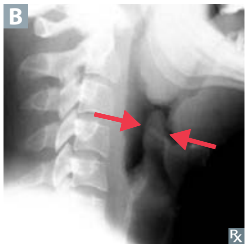
*N gonorrhoeae* is often intracellular (within neutrophils) A.

Acid production: meningococci—maltose and glucose; gonococci—glucose.

| Gonococci | Meningococci |
|---|---|
| No polysaccharide capsule | Polysaccharide capsule |
| No maltose acid detection | Maltose acid detection |
| No vaccine due to antigenic variation of pilus proteins | Vaccine (type B vaccine available for at-risk individuals) |
| Sexually or perinatally transmitted | Transmitted via respiratory and oral secretions. More common among individuals in close quarters (eg, army barracks, college dorms) |
| Causes gonorrhea, septic arthritis, neonatal conjunctivitis (2–5 days after birth), pelvic inflammatory disease (PID), and Fitz-Hugh–Curtis syndrome | Causes meningococcemia with petechial hemorrhages and gangrene of toes B, meningitis, Waterhouse-Friderichsen syndrome (adrenal insufficiency, fever, DIC) |
| Diagnosed with NAT | Diagnosed via culture-based tests or PCR |
| Condoms ↓ sexual transmission, erythromycin eye ointment prevents neonatal blindness | Rifampin, ciprofloxacin, or ceftriaxone prophylaxis in close contacts |
| Treatment: ceftriaxone + azithromycin (to cover possible chlamydial coinfection, ceftriaxone-resistant strains) | Treatment: ceftriaxone or penicillin G |

## Haemophilus influenzae




Small gram ⊖ (coccobacillary) rod. Aerosol transmission. Nontypeable (unencapsulated) strains are the most common cause of mucosal infections (otitis media, conjunctivitis, bronchitis) as well as invasive infections since the vaccine for capsular type b was introduced. Produces IgA protease.

Culture on chocolate agar, which contains factors V ($NAD^+$) and X (hematin) for growth; can also be grown with *S aureus*, which provides factor V via RBC hemolysis.

*Haemophilus* causes epiglottitis (endoscopic appearance in A, can be "cherry red" in children; "thumb sign" on lateral neck x-ray B), meningitis, otitis media, and pneumonia.

Vaccine contains type b capsular polysaccharide (polyribosylribitol phosphate) conjugated to diphtheria toxoid or other protein. Given between 2 and 18 months of age.

Does not cause the flu (influenza virus does).

Treatment: amoxicillin +/– clavulanate for mucosal infections; ceftriaxone for meningitis; rifampin prophylaxis for close contacts.

## Burkholderia cepacia complex

Gram ⊖ bacilli. Causes pneumonia in and can be transmitted between patients with cystic fibrosis. Often multidrug resistant. Infection is a relative contraindication to undergoing lung transplant due to its association with poor outcomes.

### *Bordetella pertussis*

Gram ⊖, aerobic coccobacillus. Virulence factors include pertussis toxin (disables $G_i$), adenylate cyclase toxin (↑ cAMP), and tracheal cytotoxin. Three clinical stages:

- **C**atarrhal—low-grade fevers, **c**oryza.
- **P**aroxysmal—paroxysms of intense cough followed by inspiratory "whoo**p**" ("whooping cough"), posttussive vomiting.
- Convalescent—gradual recovery of chronic cough.

Prevented by Tdap, DTaP vaccines.
Treatment: macrolides; if allergic use TMP-SMX.

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### *Brucella*

Gram ⊖, aerobic coccobacillus. Transmitted via ingestion of contaminated animal products (eg, **un**pasteurized milk). Survives in macrophages in the reticuloendothelial system. Can form non-caseating granulomas. Typically presents with **un**dulant fever, night sweats, and arthralgia.
Treatment: doxycycline + rifampin or streptomycin.

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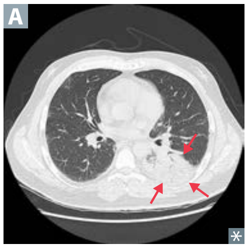
### *Legionella pneumophila*



Gram ⊖ rod. Gram stains poorly—use **silver** stain. Grow on **charcoal** yeast extract medium with **iron** and **cysteine**. Detected by presence of antigen in urine. Labs may show hyponatremia.
Aerosol transmission from environmental water source habitat (eg, air conditioning systems, hot water tanks). Outbreaks associated with cruise ships, nursing homes. No person-to-person transmission.
Treatment: macrolide or quinolone.

Think of a French **legionnaire** (soldier) with his **silver** helmet, sitting around a campfire (**charcoal**) with his **iron** dagger—he is missing his **sister** (cysteine).
Legionnaires' disease—severe pneumonia (often unilateral and lobar A), fever, GI and CNS symptoms. Risk factors include older age, tobacco smoking, chronic lung disease.
Pontiac fever—mild flu-like symptoms.

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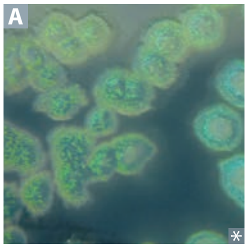
### *Pseudomonas aeruginosa*



*Aeruginosa*—**aer**obic; motile, catalase ⊕, gram ⊖ rod. Non-lactose fermenting. Oxidase ⊕. Frequently found in water. Has a grape-like odor.
**PSEUDOMONAS** is associated with: **P**neumonia, **S**epsis, **E**cthyma gangrenosum, **U**TIs, **D**iabetes, **O**steomyelitis, **M**ucoid polysaccharide capsule, **O**titis externa (swimmer's ear), **N**osocomial infections (eg, catheters, equipment), **A**ddiction (people who inject drugs), **S**kin infections (eg, hot tub folliculitis, wound infection in burn victims).
Mucoid polysaccharide capsule may contribute to chronic pneumonia in patients with cystic fibrosis due to biofilmformation.
Produces **PEEP**: **P**hospholipase C (degrades cell membranes); **E**ndotoxin (fever, shock); **E**xotoxin A (inactivates EF-2); **P**igments: pyoverdine and pyocyanin (blue-green pigment A; also generates ROS).

Corneal ulcers/keratitis in contact lens wearers/minor eye trauma.
Ecthyma gangrenosum—rapidly progressive, necrotic cutaneous lesion B caused by *Pseudomonas* bacteremia. Typically seen in immunocompromised patients.
Treatments:

- Antipseudomonal penicillins in combination with β-lactamase inhibitor (eg, piperacillin-tazobactam)
- 3rd- and 4th-generation cephalosporins (eg, ceftazidime, cefepime)
- Monobactams
- Fluoroquinolones
- Carbapenems

## *Salmonella* vs *Shigella*

Both *Salmonella* and *Shigella* are gram ⊖ rods, non-lactose fermenters, oxidase ⊖, and can invade the GI tract via M cells of Peyer patches.

| | ***Salmonella typhi*** **(ty-Vi)** | ***Salmonella*** **spp. except** ***S typhi*** | ***Shigella*** |
|---|---|---|---|
| RESERVOIRS | Humans only | Humans and animals | Humans only |
| SPREAD | Hematogenous spread | Hematogenous spread | Cell to cell; no hematogenous spread |
| $H_2S$ PRODUCTION | Yes | Yes | No |
| FLAGELLA | Yes (**salmon swim**) | Yes (**salmon swim**) | No |
| VIRULENCE FACTORS | Endotoxin; **Vi** capsule (pronounce "ty**Vi**") | Endotoxin | Endotoxin; Shiga toxin (enterotoxin) |
| INFECTIOUS DOSE ($ID_{50}$) | High—large inoculum required; acid-labile (inactivated by gastric acids) | High | Low—very small inoculum required; acid stable (resistant to gastric acids) |
| EFFECT OF ANTIBIOTICS ON FECAL EXCRETION | Prolongs duration | Prolongs duration | Shortens duration |
| IMMUNE RESPONSE | Primarily monocytes | PMNs in disseminated disease | Primarily PMN infiltration |
| GI MANIFESTATIONS | Constipation, followed by diarrhea | Diarrhea (possibly bloody) | Crampy abdominal pain → tenesmus, bloody mucoid stools (bacillary dysentery) |
| VACCINE | Oral vaccine contains live attenuated *S typhi*<br>IM vaccine contains Vi capsular polysaccharide | No vaccine | No vaccine |
| UNIQUE PROPERTIES | ▪ Causes typhoid fever (rose spots on abdomen, constipation, abdominal pain, fever [pulse-temperature dissociation]; later GI ulceration and hemorrhage); treat with ceftriaxone or fluoroquinolone<br>▪ Carrier state with gallbladder colonization | ▪ Poultry, eggs, pets, and turtles are common sources<br>▪ Antibiotics not indicated<br>▪ Gastroenteritis is usually caused by non-typhoidal *Salmonella* | ▪ **4 F**'s: **f**ingers, **f**lies, **f**ood, **f**eces<br>▪ In order of decreasing severity (less toxin produced): *S dysenteriae*, *S flexneri*, *S boydii*, *S sonnei*<br>▪ Invasion of M cells is key to pathogenicity: organisms that produce little toxin can cause disease |

## *Yersinia enterocolitica*

Gram ⊖ pleomorphic rod/coccobacillus. Usually transmitted from pet feces (eg, cats, dogs), contaminated milk, or pork. Can cause acute bloody diarrhea, pseudoappendicitis (right lower abdominal pain due to mesenteric adenitis and/or terminal ileitis), reactive arthritis in adults.

## Lactose-fermenting enteric bacteria

Fermentation of **lactose** → pink colonies on Mac**Con**key agar. Examples include ***C****itrobacter*, ***E*** *coli*, ***E****nterobacter*, ***K****lebsiella*, ***S****erratia*. *E coli* produces β-galactosidase, which breaks down lactose into glucose and galactose.

Mc**Cow**key **CEEKS** milk.

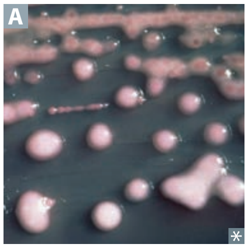
EMB agar—lactose fermenters grow as purple/black colonies. *E coli* grows colonies with a green sheen.

***Escherichia coli***

Gram ⊖, indole ⊕ rod. *E coli* virulence factors: fimbriae—cystitis and pyelonephritis (P pili); K capsule—pneumonia, neonatal meningitis; LPS endotoxin—septic shock.

| STRAIN | TOXIN AND MECHANISM | PRESENTATION |
|---|---|---|
| **Enteroinvasive *E coli*** | Microbe invades intestinal mucosa and causes necrosis and inflammation. | EIEC is Invasive; dysentery. Clinical manifestations similar to *Shigella*. |
| **Enterotoxigenic *E coli*** | Produces heat-labile and heat-stable enteroToxins. No inflammation or invasion. | ETEC; Traveler's diarrhea (watery). |
| **Enteropathogenic *E coli*** | No toxin produced. Adheres to apical surface, flattens villi, prevents absorption. | Diarrhea, usually in children (think EPEC and Pediatrics). |
| **Enterohemorrhagic *E coli*** | O157:H7 is most common serotype in US. Often transmitted via undercooked meat, raw leafy vegetables.<br>Shiga toxin causes hemolytic-uremic syndrome—triad of anemia, thrombocytopenia, and acute kidney injury due to microthrombi forming on damaged endothelium → mechanical hemolysis (with schistocytes on peripheral blood smear), platelet consumption, and ↓ renal blood flow. | Dysentery (toxin alone causes necrosis and inflammation).<br>Does not ferment sorbitol (vs other *E coli*).<br>EHEC associated with hemorrhage, hamburgers, hemolytic-uremic syndrome. |

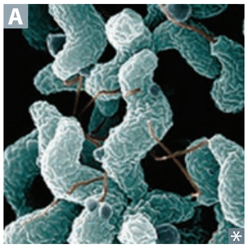
***Klebsiella***



Gram ⊖ rod; intestinal flora that causes lobar pneumonia in patients with alcohol overuse and patients with diabetes when aspirated. Very mucoid colonies A caused by abundant polysaccharide capsules. Dark red "currant jelly" sputum (blood/mucus).
Also cause of nosocomial UTIs. Associated with evolution of multidrug resistance (MDR).

ABCDE's of Klebsiella:
- Aspiration pneumonia
- aBscess in lungs and liver
- "Currant jelly" sputum
- Diabetes mellitus
- EtOH overuse

***Campylobacter jejuni***



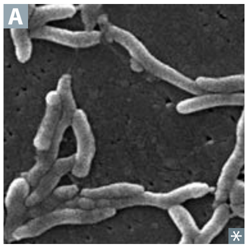
Gram ⊖, comma or S shaped (with polar flagella) A, oxidase ⊕, grows at 42°C ("*Campylobacter* likes the hot campfire").
Major cause of bloody diarrhea, especially in children. Fecal-oral transmission through person-to-person contact or via ingestion of undercooked contaminated poultry or meat, unpasteurized milk. Contact with infected animals (dogs, cats, pigs) is also a risk factor.
Common antecedent to Guillain-Barré syndrome and reactive arthritis.

### *Vibrio cholerae*


Gram $\ominus$, flagellated, comma shaped A, oxidase $\oplus$, grows in alkaline media. Endemic to developing countries. Produces profuse rice-water diarrhea via enterotoxin that permanently activates $G_s$, ↑ cAMP. Sensitive to stomach acid (acid labile); requires large inoculum (high $ID_{50}$) unless host has ↓ gastric acidity. Transmitted via ingestion of contaminated water or uncooked food (eg, raw shellfish). Treat promptly with oral rehydration solution.

*Vibrio vulnificus*—gram $\ominus$ bacillus, usually found in marine environments. Causes severe wound infections or septicemia due to exposure to contaminated sea water. Presents as cellulitis that can progress to necrotizing fasciitis in high-risk patients, especially those with liver disease (eg, cirrhosis). Serious wound infection requires surgical debridement.

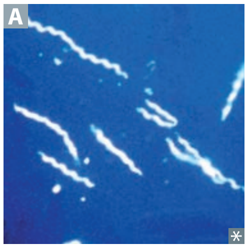
### *Helicobacter pylori*




Curved, flagellated (motile), gram $\ominus$ rod A that is **triple** $\oplus$: catalase $\oplus$, oxidase $\oplus$, and urease $\oplus$ (can use urea breath test or fecal antigen test for diagnosis). Urease produces ammonia, creating an alkaline environment, which helps *H pylori* survive in acidic mucosa. Colonizes mainly antrum of stomach; causes gastritis and peptic ulcers (especially duodenal). Risk factor for peptic ulcer disease, gastric adenocarcinoma, and MALT lymphoma.

Most common initial treatment is **triple** therapy: **a**moxicillin (metronidazole if penicillin allergy) + **c**larithromycin + **p**roton pump inhibitor; **a**ntibiotics **c**ure ***P**ylori*. Bismuth-based quadruple therapy if concerned about macrolide resistance.

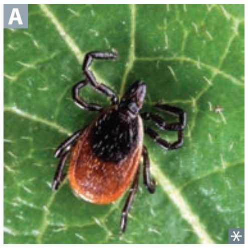
### Spirochetes




Spiral-shaped bacteria A with axial filaments. Includes ***L**eptospira*, ***T**reponema*, and ***B**orrelia*. Only *Borrelia* can be visualized using aniline dyes (Wright or Giemsa stain) in light microscopy due to size. *Treponema* is visualized by dark-field microscopy or direct fluorescent antibody (DFA) microscopy.

**L**ittle **T**wirling **B**acteria

### Lyme disease





Caused by *Borrelia burgdorferi*, which is transmitted by the *Ixodes* deer tick A (also vector for *Anaplasma* spp. and protozoa *Babesia*). Natural reservoir is the mouse; deer are essential to tick life cycle but do not harbor *Borrelia*.

Common in northeastern United States.

Stage 1—early localized: erythema migrans (typical "bulls-eye" configuration B is pathognomonic but not always present), flu-like symptoms.

Stage 2—early disseminated: secondary lesions, carditis, AV block, facial nerve (Bell) palsy, migratory myalgias/transient arthritis.

Stage 3—late disseminated: encephalopathy, chronic arthritis, peripheral neuropathy.

A Key **Lyme** pie to the **FACE**:
- **F**acial nerve palsy (typically bilateral)
- **A**rthritis
- **C**ardiac block
- **E**rythema migrans

Treatment: doxycycline (1st line); amoxicillin (pregnant patients, children < 8 years old); ceftriaxone if IV therapy required

**_Leptospira interrogans_**

Spirochete with hook-shaped ends found in water contaminated with animal urine.

**Leptospirosis**—flu-like symptoms, myalgias (classically of calves), jaundice, photophobia with conjunctival suffusion (erythema without exudate). Prevalent among surfers and in tropics (eg, Hawaii).

**Weil disease** (icterohemorrhagic leptospirosis)—severe form with jaundice and azotemia from liver and kidney dysfunction, fever, hemorrhage, and anemia.

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**Syphilis**

Caused by spirochete *Treponema pallidum*. Treatment: penicillin G.

**Primary syphilis**

Localized disease presenting with **painless** chancre A. Use fluorescent or dark-field microscopy to visualize treponemes in fluid from chancre B. VDRL ⊕ in ~ 80%.

**Secondary syphilis**

Disseminated disease with constitutional symptoms, maculopapular rash C (including palms D and soles), condylomata lata E (smooth, painless, wart-like white lesions on genitals), lymphadenopathy, patchy hair loss; also confirmable with dark-field microscopy.
Serologic testing: VDRL/RPR (nonspecific), confirm diagnosis with specific test (eg, FTA-ABS).
Secondary syphilis = systemic. Latent syphilis (⊕ serology without symptoms) may follow.

**Tertiary syphilis**

Gummas F (chronic granulomas), aortitis (vasa vasorum destruction), neurosyphilis (tabes dorsalis, "general paresis"), Argyll Robertson pupil (constricts with accommodation but is not reactive to light).
Signs: broad-based ataxia, ⊕ Romberg, Charcot joint, stroke without hypertension.
For neurosyphilis: test spinal fluid with VDRL, FTA-ABS, and PCR.

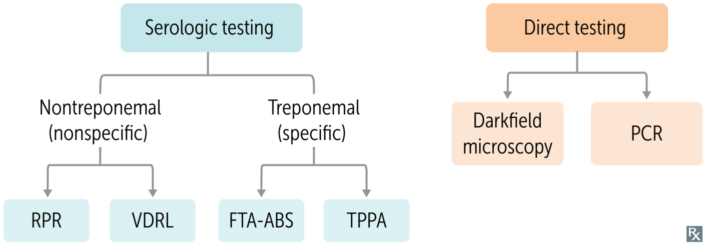
**Congenital syphilis**

Presents with facial abnormalities such as rhagades (linear scars at angle of mouth, black arrow in G), snuffles (nasal discharge, red arrow in G), saddle nose, notched (Hutchinson) teeth H, mulberry molars, and short maxilla; saber shins; CN VIII deafness.
To prevent, treat patient early in pregnancy, as placental transmission typically occurs after first trimester.

### Diagnosing syphilis

VDRL and RPR detects nonspecific antibody that reacts with beef cardiolipin. Quantitative, inexpensive, and widely available test for syphilis (sensitive but not specific).

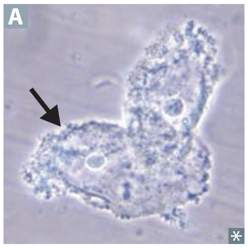
False-**P**ositive results on **VDRL** with:
- **P**regnancy
- **V**iral infection (eg, EBV, hepatitis)
- **D**rugs (eg, chlorpromazine, procainamide)
- **R**heumatic fever (rare)
- **L**upus (anticardiolipin antibody) and **L**eprosy




### Jarisch-Herxheimer reaction

Flu-like symptoms (fever, chills, headache, myalgia) after antibiotics are started due to host response to sudden release of bacterial antigens.

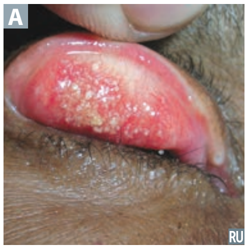
### *Gardnerella vaginalis*




A pleomorphic, gram-variable rod involved in bacterial vaginosis. Presents as a gray vaginal discharge with a fishy smell; nonpainful (vs vaginitis). Associated with sexual activity, but not sexually transmitted. Bacterial vaginosis is also characterized by overgrowth of certain anaerobic bacteria in vagina (due to ↓ lactobacilli). Clue cells (vaginal epithelial cells covered with *Gardnerella*) have stippled appearance along outer margin (arrow in A).

Amine whiff test—mixing discharge with 10% KOH enhances fishy odor.
Vaginal pH >4.5 during infection.
Treatment: metronidazole or clindamycin.

### Chlamydiae




Chlamydiae cannot make their own ATP. They are obligate intracellular organisms that cause mucosal infections. 2 forms:
- **E**lementary body (small, dense) is "**e**nfectious" and **e**nters cell via **e**ndocytosis; transforms into reticulate body.
- **R**eticulate body **r**eplicates in cell by fission; **r**eorganizes into elementary bodies.

*Chlamydia trachomatis* causes neonatal and follicular adult conjunctivitis A, nongonococcal urethritis, PID, and reactive arthritis.
*Chlamydophila pneumoniae* and *Chlamydophila psittaci* cause atypical pneumonia; transmitted by aerosol.

Chlamydial cell wall lacks classic peptidoglycan (due to reduced muramic acid), rendering β-lactam antibiotics ineffective.
*Chlamys* = cloak (intracellular).
*C psittaci*—has an avian reservoir (**p**arrots), causes atypical **p**neumonia.
Lab diagnosis: PCR, nucleic acid amplification test. Cytoplasmic inclusions (reticulate bodies) seen on Giemsa or fluorescent antibody–stained smear.
Treatment: azithromycin (favored because one-time treatment) or doxycycline. Add ceftriaxone for possible concomitant gonorrhea.

### *Chlamydia trachomatis* serotypes

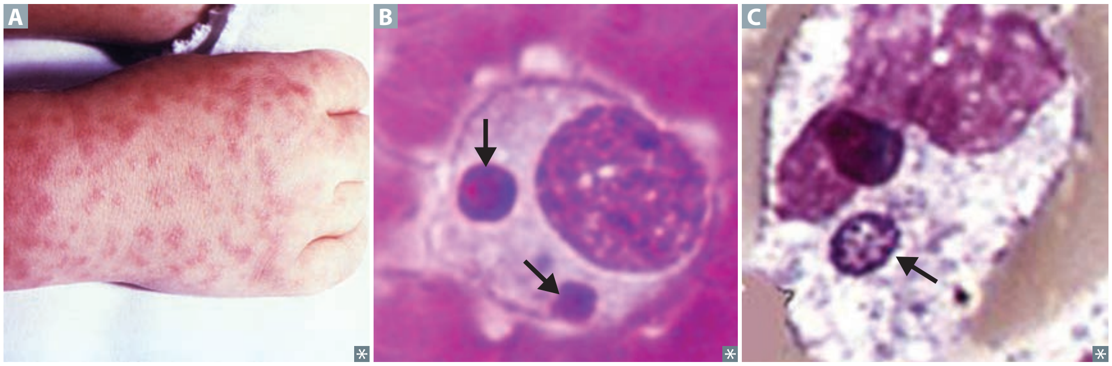
| | | |
|---|---|---|
| Types A, B, and C | Chronic infection, cause blindness due to follicular conjunctivitis in resource-limited areas. | ABC = Africa, Blindness, Chronic infection. |
| Types D–K | Urethritis/PID, ectopic pregnancy, neonatal pneumonia (staccato cough) with eosinophilia, neonatal conjunctivitis (1–2 weeks after birth). | D–K = everything else. Neonatal disease can be acquired during vaginal birth if pregnant patient is infected. |
| Types L1, L2, and L3 | Lymphogranuloma venereum—small, painless ulcers on genitals → swollen, painful inguinal lymph nodes that ulcerate (buboes). Treat with doxycycline. | |

### Zoonotic bacteria

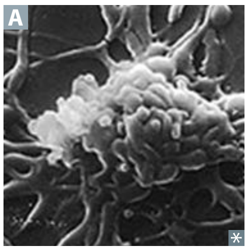
Zoonosis—infectious disease transmitted between animals and humans.

| SPECIES | DISEASE | TRANSMISSION AND SOURCE |
|---|---|---|
| *Anaplasma* spp | Anaplasmosis | *Ixodes* ticks (live on deer and mice) |
| *Bartonella* spp | Cat scratch disease, bacillary angiomatosis | Cat scratch |
| *Borrelia burgdorferi* | Lyme disease | *Ixodes* ticks (live on deer and mice) |
| *Borrelia recurrentis* | Relapsing fever | Louse (recurrent due to variable surface antigens) |
| *Brucella* spp | Brucellosis/undulant fever | Unpasteurized dairy |
| *Campylobacter* | Bloody diarrhea | Feces from infected pets/animals; contaminated meats/foods/hands |
| *Chlamydophila psittaci* | Psittacosis | Parrots, other birds |
| *Coxiella burnetii* | Q fever | Aerosols of cattle/sheep amniotic fluid |
| *Ehrlichia chaffeensis* | Ehrlichiosis | *Amblyomma* (Lone Star tick) |
| *Francisella tularensis* | Tularemia | Ticks, rabbits, deer flies |
| *Leptospira* spp | Leptospirosis | Animal urine in water; recreational water use |
| *Mycobacterium leprae* | Leprosy | Humans with lepromatous leprosy; armadillo (rare) |
| *Pasteurella multocida* | Cellulitis, osteomyelitis | Animal bite, cats, dogs |
| *Rickettsia prowazekii* | Epidemic typhus | Human to human via human body louse |
| *Rickettsia rickettsii* | Rocky Mountain spotted fever | *Dermacentor* (dog tick) |
| *Rickettsia typhi* | Endemic typhus | Fleas |
| *Salmonella* spp (except *S typhi*) | Diarrhea (which may be bloody), vomiting, fever, abdominal cramps | Reptiles and poultry |
| *Yersinia pestis* | Plague | Fleas (rats and prairie dogs are reservoirs) |

| Rickettsial diseases and vector-borne illnesses | Treatment: doxycycline. | |
|---|---|---|
| RASH COMMON | | |
| **Rocky Mountain spotted fever** | *Rickettsia rickettsii*, vector is tick. Despite its name, disease occurs primarily in the South Atlantic states, especially North Carolina. Rash typically starts at wrists A and ankles and then spreads to trunk, palms, and soles. | Classic triad—headache, fever, rash (vasculitis). **Palms** and **soles** rash is seen in **C**oxsackievirus **A** infection (hand, foot, and mouth disease), **R**ocky Mountain spotted fever, and 2° **S**yphilis (you drive **CARS** using your **palms** and **soles**). |
| **Typhus** | Endemic (fleas)—*R typhi*. Epidemic (human body louse)—*R prowazekii*. Rash starts centrally and spreads out, sparing palms and soles. | ***R**ickettsii* on the w**r**ists, **t**yphus on the **t**runk. |
| RASH RARE | | |
| **Ehrlichiosis** | ***E**hrlichia*, vector is tick. **M**onocytes with morulae B (mulberry-like inclusions) in cytoplasm. | **MEGA**: **M**onocytes = **E**hrlichiosis **G**ranulocytes = **A**naplasmosis |
| **Anaplasmosis** | ***A**naplasma*, vector is tick. **G**ranulocytes with morulae C in cytoplasm. | |
| **Q fever** | *Coxiella **b**urnetii*, no arthropod vector. Bacterium inhaled as aerosols from cattle/sheep amniotic fluid. Presents with headache, cough, influenza-like symptoms, pneumonia, possibly in combination with hepatitis. Common cause of culture ⊖ endocarditis. | **Q** fever is caused by a **Q**uite **C**omplicated **b**ug because it has no rash or vector and its causative organism can survive outside in its endospore form. Not in the *Rickettsia* genus, but closely related. |



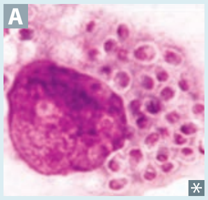
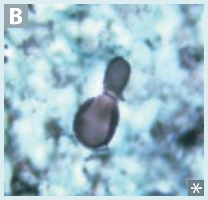
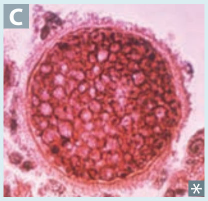
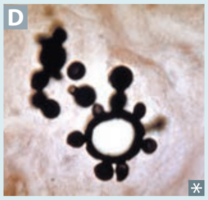

| ***Mycoplasma pneumoniae*** | Classic cause of atypical "walking pneumonia" (insidious onset, headache, nonproductive cough, patchy or diffuse interstitial infiltrate, macular rash). Occurs frequently in those <30 years old; outbreaks in military recruits, prisons, colleges. Treatment: macrolides, doxycycline, or fluoroquinolone (penicillin ineffective since *Mycoplasma* has no cell wall). | Not seen on Gram stain. Pleomorphic A. Bacterial membrane contains sterols for stability. Grown on Eaton agar. CXR appears more severe than patient presentation. High titer of **cold** agglutinins (IgM), which can agglutinate RBCs. *Mycoplasma* gets **cold** without a **coat** (no cell wall). Can cause atypical variant of Stevens-Johnson syndrome, typically in children and adolescents. |
|---|---|---|

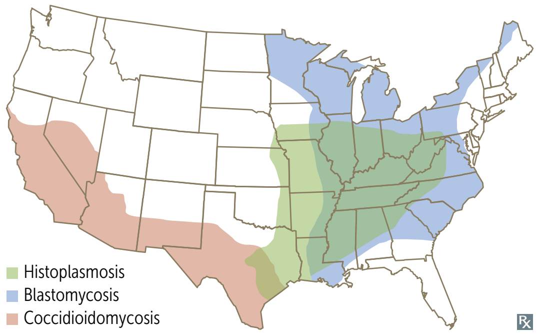


## ▸ MICROBIOLOGY—MYCOLOGY

**Systemic mycoses**

All of the following can cause pneumonia and can disseminate.
All are caused by dimorphic fungi: **cold** (20°C) = **mold**; **heat** (37°C) = **yeast**. Only exception is *Coccidioides*, which is a spherule (not yeast) in tissue.
Systemic mycoses can form granulomas (like TB); cannot be transmitted person-to-person (unlike TB).
Treatment: fluconazole or itraconazole for **local** infection; amphotericin B for **systemic** infection.

| DISEASE | ENDEMIC LOCATION | PATHOLOGIC FEATURES | UNIQUE SIGNS/SYMPTOMS | NOTES |
|---|---|---|---|---|
| **Histoplasmosis**  | Mississippi and Ohio River Valleys | Macrophage filled with *Histoplasma* (smaller than RBC) A | Palatal/tongue ulcers, splenomegaly, pancytopenia, erythema nodosum | **H**isto **h**ides (within macrophages)<br>Associated with bird or bat droppings (eg, caves)<br>Diagnosis via urine/serum antigen |
| **Blastomycosis**  | Eastern and Central US, Great Lakes | **Broad**-based budding of *Blastomyces* (same size as RBC) B | Inflammatory lung disease<br>Disseminates to bone/skin (verrucous lesions, may mimic SCC). | **Bl**asto **b**uds **broad**ly |
| **Coccidioidomycosis**  | Southwestern US, California | Spherule (much larger than RBC) filled with endospores of *Coccidioides* C | Disseminates to bone/skin<br>Erythema nodosum (desert bumps) or multiforme<br>Arthralgias (desert rheumatism)<br>Can cause meningitis | Associated with dust exposure in endemic areas (eg, archeological excavations, earthquakes) |
| **Para-coccidioidomycosis**  | **Latin America** | Budding yeast of *Paracoccidioides* with "**captain's wheel**" formation (much larger than RBC) D | Similar to blastomycosis, males > females | **Para**coccidio **para**sails with the **captain's wheel** all the way to **Latin America** |

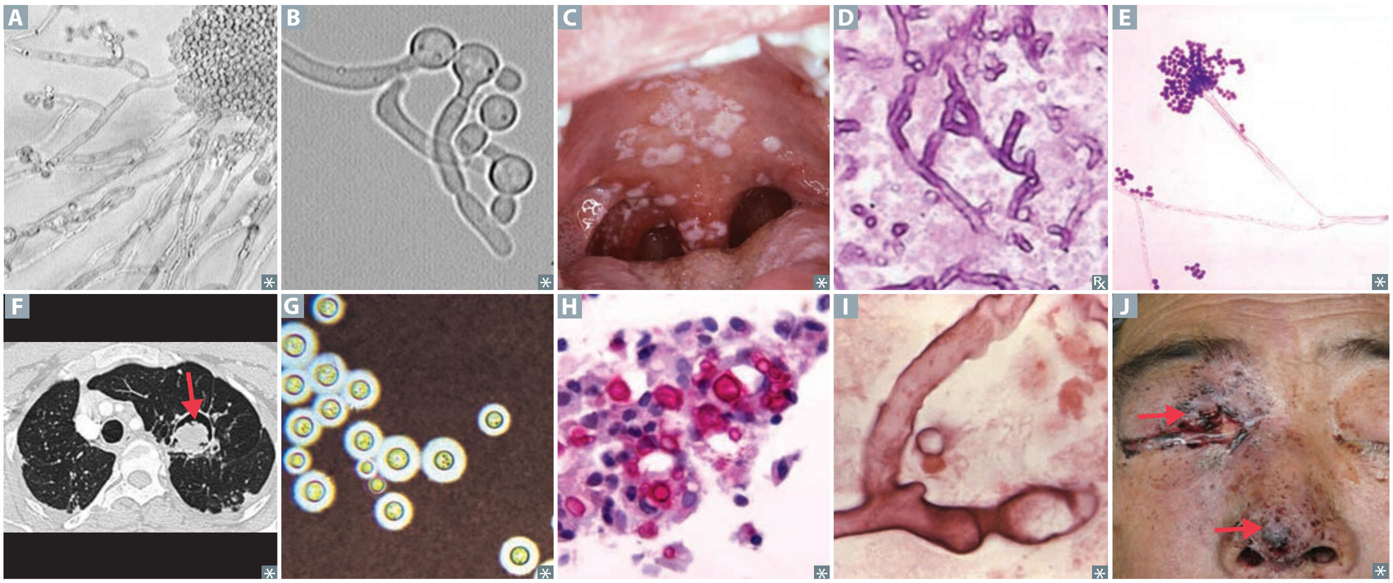


## Cutaneous mycoses

| | |
|---|---|
| **Tinea (dermatophytes)** | Clinical name for dermatophyte (cutaneous fungal) infections. Dermatophytes include *Microsporum*, *Trichophyton*, and *Epidermophyton*. Branching septate hyphae visible on KOH preparation with blue fungal stain A. Associated with pruritus. |
| Tinea capitis | Occurs on head, scalp. Associated with lymphadenopathy, alopecia, scaling B. |
| Tinea corporis | Occurs on body (usually torso). Characterized by enlarging erythematous, scaly rings ("ringworm") with central clearing C. Can be acquired from contact with infected pets or farm animals. |
| Tinea cruris | Occurs in inguinal area ("jock itch") D. Often does not show the central clearing seen in tinea corporis. |
| Tinea pedis | Three varieties ("athlete's foot"):<br>▪ Interdigital E; most common<br>▪ Moccasin distribution F<br>▪ Vesicular type |
| Tinea unguium | Onychomycosis; occurs on nails. |
| **Tinea (pityriasis) versicolor** | Caused by *Malassezia* spp. (*Pityrosporum* spp.), a yeast-like fungus (not a dermatophyte despite being called tinea). Degradation of lipids produces acids that inhibit tyrosinase (involved in melanin synthesis) → hypopigmentation G; hyperpigmentation and/or pink patches can also occur due to inflammatory response. Less pruritic than dermatophytes.<br>Can occur any time of year, but more common in summer (hot, humid weather). "Spaghetti and meatballs" appearance on microscopy H.<br>Treatment: selenium sulfide, topical and/or oral antifungal medications. |

## Opportunistic fungal infections

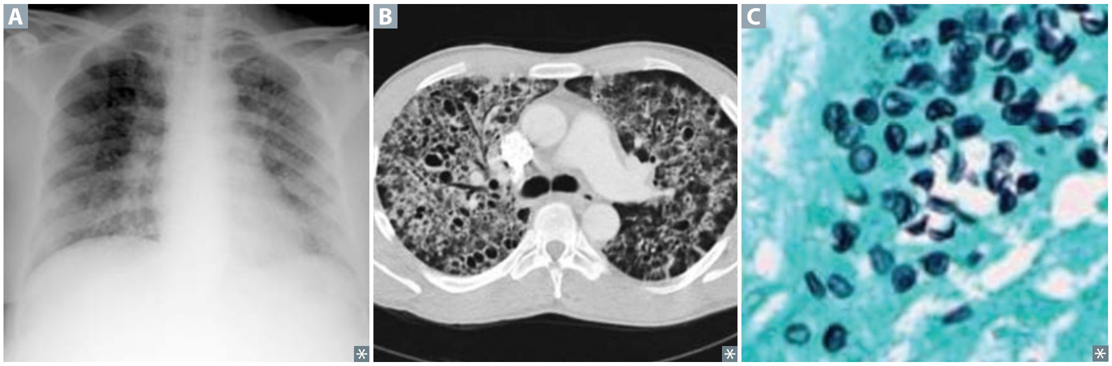
| | |
|---|---|
| ***Candida albicans*** | *alba* = white. Dimorphic; forms pseudohyphae and budding yeasts at 20°C A, germ tubes at 37°C B.<br>Systemic or superficial fungal infection. Causes oral C and esophageal thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (diabetes, use of antibiotics), diaper rash, endocarditis (people who inject drugs), disseminated candidiasis (especially in neutropenic patients), chronic mucocutaneous candidiasis.<br>Treatment: oral fluconazole/topical azoles for vaginal; nystatin, azoles, or, rarely, echinocandins for oral; fluconazole, echinocandins, or amphotericin B for esophageal or systemic disease. |
| ***Aspergillus fumigatus*** | Septate hyphae that branch at 45° **A**cute **A**ngle D E.<br>Causes invasive aspergillosis in immunocompromised patients, especially those with neutrophil dysfunction (eg, chronic granulomatous disease) because *Aspergillus* is catalase ⊕.<br>Can cause aspergillomas F in pre-existing lung cavities, especially after TB infection.<br>Some species of *Aspergillus* produce **A**flatoxins (associated with hepatocellular carcinoma).<br>Treatment: voriconazole or echinocandins (2nd-line).<br><br>Allergic bronchopulmonary aspergillosis (ABPA)—hypersensitivity response to *Aspergillus* growing in lung mucus. Associated with asthma and cystic fibrosis; may cause bronchiectasis and eosinophilia. |
| ***Cryptococcus neoformans*** | 5–10 μm with narrow budding. Heavily encapsulated yeast. Not dimorphic.<br>Found in soil, pigeon droppings. Acquired through inhalation with hematogenous dissemination to meninges. Highlighted with India ink (clear halo G) and mucicarmine (red inner capsule H). Latex agglutination test detects polysaccharide capsular antigen and is more sensitive and specific.<br>Causes cryptococcosis, cryptococcal meningitis, cryptococcal encephalitis (“soap bubble” lesions in brain), primarily in immunocompromised.<br>Treatment: amphotericin B + flucytosine followed by fluconazole for cryptococcal meningitis. |
| ***Mucor* and *Rhizopus* spp** | Irregular, broad, nonseptate hyphae branching at wide angles I.<br>Causes mucormycosis, mostly in patients with DKA and/or neutropenia (eg, leukemia). Inhalation of spores → fungi proliferate in blood vessel walls, penetrate cribriform plate, and enter brain. Rhinocerebral, frontal lobe abscess; cavernous sinus thrombosis. Headache, facial pain, black necrotic eschar on face J; may have cranial nerve involvement.<br>Treatment: surgical debridement, amphotericin B or isavuconazole. |



***Pneumocystis jirovecii***

Causes *Pneumocystis* pneumonia (PCP), a diffuse interstitial pneumonia A. Yeast-like fungus (originally classified as protozoan). Most infections are asymptomatic. Immunosuppression (eg, AIDS) predisposes to disease. Diffuse, bilateral ground-glass opacities on chest imaging, with pneumatoceles B. Diagnosed by bronchoalveolar lavage or lung biopsy. Disc-shaped yeast seen on methenamine silver stain of lung tissue C or with fluorescent antibody.

Treatment/prophylaxis: TMP-SMX, pentamidine, dapsone (prophylaxis as single agent, or treatment in combination with TMP), atovaquone. Start prophylaxis when CD4+ cell count drops to < 200 cells/mm$^3$ in people living with HIV.

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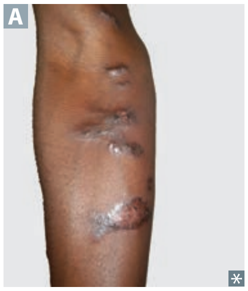
***Sporothrix schenckii***




Causes sporotrichosis. Dimorphic fungus. Exists as a **cigar**-shaped yeast at 37 °C in the human body and as hyphae with spores in soil (conidia). Lives on vegetation. When spores are traumatically introduced into the skin, typically by a thorn ("**rose gardener**'s disease"), causes local pustule or ulcer with nodules along draining lymphatics (ascending lymphangitis A). Disseminated disease possible in immunocompromised host.

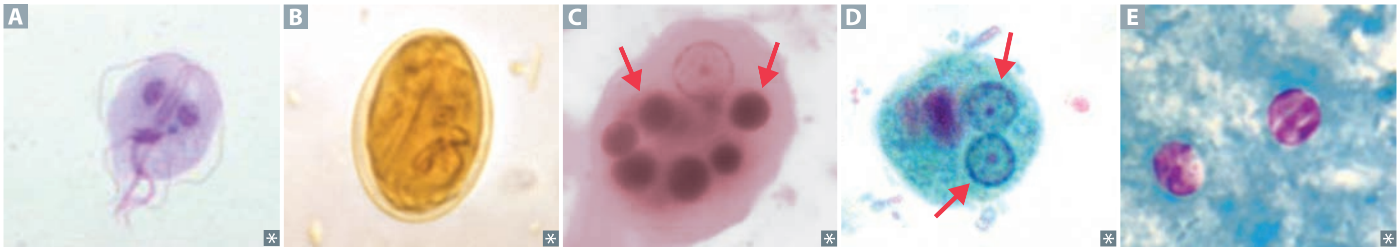
Treatment: itraconazole or **pot**assium iodide (only for cutaneous/lymphocutaneous).

Think of a **rose gardener** who smokes a **cigar** and **pot**.

## ▶ MICROBIOLOGY—PARASITOLOGY

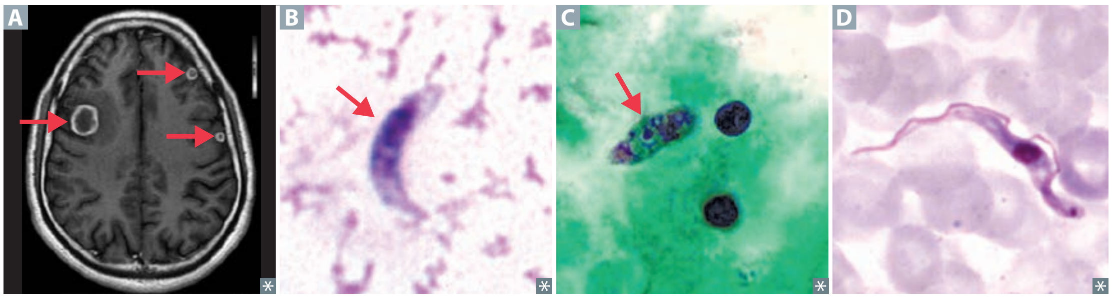
### Protozoa—gastrointestinal infections

| ORGANISM | DISEASE | TRANSMISSION | DIAGNOSIS | TREATMENT |
|---|---|---|---|---|
| ***Giardia lamblia*** | **Giardiasis**—bloating, flatulence, foul-smelling, nonbloody, fatty diarrhea (often seen in campers/hikers)—think fat-rich Ghirardelli chocolates for fatty stools of *Giardia* | Cysts in water | Multinucleated trophozoites A or cysts B in stool, antigen detection, PCR | Metronidazole |
| ***Entamoeba histolytica*** | **Amebiasis**—bloody diarrhea (dysentery), liver abscess ("anchovy paste" exudate), RUQ pain; histology of colon biopsy shows flask-shaped ulcers | Cysts in water | Serology, antigen testing, PCR, and/or trophozoites (with engulfed RBCs C in the cytoplasm) or cysts with up to 4 nuclei in stool D; *Entamoeba* Eats Erythrocytes | Metronidazole; paromomycin or iodoquinol for asymptomatic cyst passers |
| ***Cryptosporidium*** | Severe diarrhea in AIDS<br>Mild disease (watery diarrhea) in immunocompetent hosts | Oocysts in water | Oocysts on acid-fast stain E, antigen detection, PCR | Prevention (by filtering city water supplies); nitazoxanide in immunocompetent hosts |

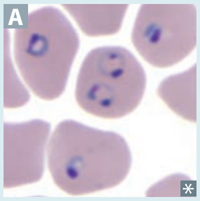
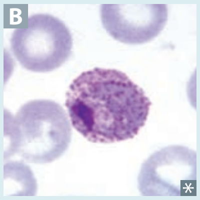
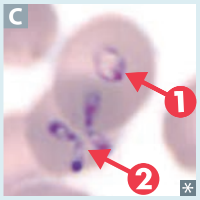


## Protozoa—CNS infections

| ORGANISM | DISEASE | TRANSMISSION | DIAGNOSIS | TREATMENT |
|---|---|---|---|---|
| ***Toxoplasma gondii*** | Immunocompetent: mononucleosis-like symptoms, ⊖ heterophile antibody test<br>Reactivation in AIDS → brain abscesses usually seen as multiple ring-enhancing lesions on MRI A<br>Congenital toxoplasmosis: classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications | Cysts in meat (most common); oocysts in cat feces; crosses placenta (pregnant patients should avoid cats) | Serology, biopsy (tachyzoite) B; PCR of amniotic fluid for possible intrauterine disease | Sulfadiazine + pyrimethamine<br>Prophylaxis with TMP-SMX when CD4+ cell count < 100 cells/mm$^3$ |
| ***Naegleria fowleri*** | Rapidly fatal meningoencephalitis | Swimming in warm freshwater; enters via cribriform plate | Amoebas in CSF C | Amphotericin B has been effective for a few survivors |
| ***Trypanosoma brucei*** | **African sleeping sickness**—enlarged lymph nodes, recurring fever (due to antigenic variation), somnolence, coma | Tsetse fly, a painful bite | Trypomastigote in blood smear D | Suramin for blood-borne disease or melarsoprol for CNS penetration ("I sure am mellow when I'm sleeping") |

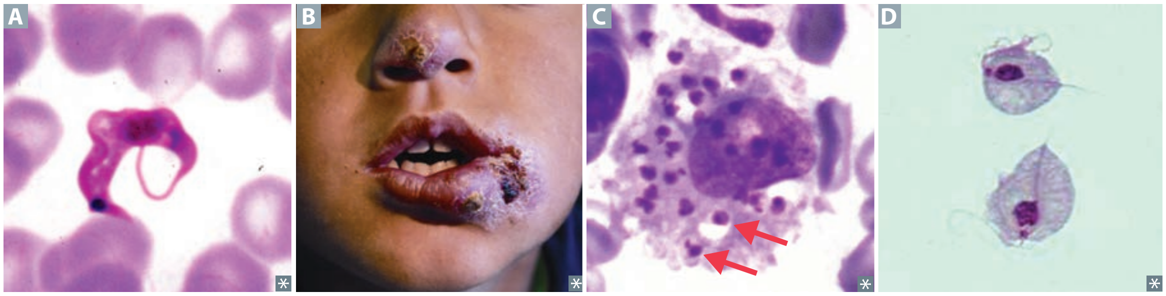


## Protozoa—hematologic infections

| ORGANISM | DISEASE | TRANSMISSION | DIAGNOSIS | TREATMENT |
|---|---|---|---|---|
| ***Plasmodium***<br>***P vivax/ovale***<br>***P falciparum***<br>***P malariae***<br><br> | **Malaria**—fever, headache, anemia, splenomegaly; hypoglycemia in severe disease<br>*P vivax/ovale*—48-hr cycle (tertian; includes fever on first day and third day, thus fevers are actually 48 hr apart); dormant form (hypnozoite) in liver<br>*P falciparum*—severe; irregular fever patterns; parasitized RBCs occlude capillaries in brain (cerebral malaria), kidneys, lungs<br>*P malariae*—72-hr cycle (quartan) | *Anopheles* mosquito | Blood smear: trophozoite ring form within RBC A, schizont containing merozoites; red granules (Schüffner stippling) B throughout RBC cytoplasm seen with *P vivax/ovale* | Chloroquine (for sensitive species); if resistant, use mefloquine or atovaquone/proguanil<br>If life-threatening, use intravenous quinidine or artesunate (test for G6PD deficiency)<br>For *P vivax/ovale*, add primaquine for hypnozoite (test for G6PD deficiency) |
| ***Babesia***<br> | **Babesiosis**—fever and hemolytic anemia; predominantly in northeastern and north central United States; asplenia ↑ risk of severe disease due to inability to clear infected RBCs | *Ixodes* tick (also vector for *Borrelia burgdorferi* and *Anaplasma* spp) | Blood smear: ring form C1, "Maltese cross" C2; PCR | Atovaquone + azithromycin |

## Protozoa—others

| ORGANISM | DISEASE | TRANSMISSION | DIAGNOSIS | TREATMENT |
|---|---|---|---|---|
| **Visceral infections** | | | | |
| ***Trypanosoma cruzi*** | **Chagas disease**—dilated cardiomyopathy with apical atrophy, megacolon, megaesophagus; predominantly in South America<br>Unilateral periorbital swelling (Romaña sign) characteristic of acute stage | Triatomine insect (kissing bug) bites and defecates around the mouth or eyes → fecal transmission into bite site or mucosa | Trypomastigote in blood smear A | **Benz**nidazole or ni**fur**timox; **cruz**ing in my **Benz**, with a **fur** coat on |
| ***Leishmania* spp** | **Visceral leishmaniasis (kala-azar)**—spiking fevers, hepatosplenomegaly, pancytopenia<br>**Cutaneous leishmaniasis**—skin ulcers B | Sandfly | Macrophages containing amastigotes C | Amphotericin B, sodium stibogluconate |
| **Sexually transmitted infections** | | | | |
| ***Trichomonas vaginalis*** | **Vaginitis**—foul-smelling, greenish discharge; itching and burning; do not confuse with *Gardnerella vaginalis*, a gram-variable bacterium associated with bacterial vaginosis | Sexual (cannot exist outside human because it cannot form cysts) | Trophozoites (motile) D on wet mount; punctate cervical hemorrhages ("strawberry cervix") | Metronidazole for patient and partner(s) (prophylaxis; check for STI) |




**Nematode routes of infection**

Ingested—*Enterobius*, *Ascaris*, *Toxocara*, *Trichinella*, *Trichuris* — You'll get sick if you **EATTT** these!

Cutaneous—*Strongyloides*, *Ancylostoma*, *Necator* — These get into your feet from the **SAN**d

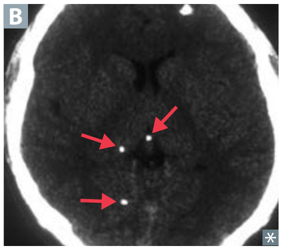
Bites—*Loa loa*, *Onchocerca volvulus*, *Wuchereria bancrofti* — Lay **LOW** to avoid getting bitten

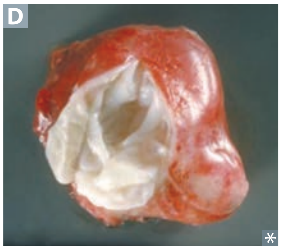
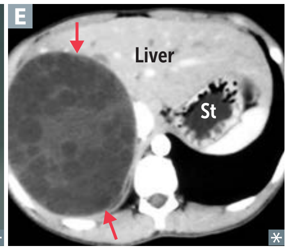
### Nematodes (roundworms)

| ORGANISM | DISEASE | TRANSMISSION | TREATMENT |
|---|---|---|---|
| **Intestinal** | | | |
| ***Enterobius vermicularis*** **(pinworm)** | Causes anal pruritus (diagnosed by seeing egg A via the tape test). | Fecal-oral. | Bendazoles, pyrantel pamoate. |
| ***Ascaris lumbricoides*** **(giant roundworm)** | May cause obstruction at ileocecal valve, biliary obstruction, intestinal perforation, migrates from nose/mouth. Migration of larvae to alveoli → Löeffler syndrome (pulmonary eosinophilia). | Fecal-oral; knobby-coated, oval eggs seen in feces under microscope B. | Bendazoles. |
| ***Strongyloides stercoralis*** **(threadworm)** | GI (eg, duodenitis), pulmonary (eg, dry cough, hemoptysis), and cutaneous (eg, pruritus) symptoms. Hyperinfection syndrome caused by autoinfection (larvae enter bloodstream). | Larvae in soil penetrate skin; rhabditiform larvae seen in feces under microscope. | Ivermectin or bendazoles. |
| ***Ancylostoma*** **spp,** ***Necator americanus*** **(hookworms)** | Cause microcytic anemia by sucking blood from intestinal wall. Cutaneous larva migrans—pruritic, serpiginous rash C. | Larvae penetrate skin from walking barefoot on contaminated beach/soil. | Bendazoles or pyrantel pamoate. |
| ***Trichinella spiralis*** | Larvae enter bloodstream, encyst in striated muscle D → myositis. Trichinosis—fever, vomiting, nausea, periorbital edema, myalgia. | Undercooked meat (especially pork); fecal-oral (less likely). | Bendazoles. |
| ***Trichuris trichiura*** **(whipworm)** | Often asymptomatic; loose stools, anemia, rectal prolapse in children. | Fecal-oral. | Bendazoles. |
| **Tissue** | | | |
| ***Toxocara canis*** | Visceral larva migrans—migration into blood → inflammation of liver, eyes (visual impairment, blindness), CNS (seizures, coma), heart (myocarditis). Patients often asymptomatic. | Fecal-oral. | Bendazoles. |
| ***Onchocerca volvulus*** | Skin changes, loss of elastic fibers, river blindness (black skin nodules, "black sight"); allergic reaction possible. | Female black fly. | Ivermectin (ivermectin for river blindness). |
| ***Loa loa*** | Swelling in skin, worm in conjunctiva. | Deer fly, horse fly, mango fly. | Diethylcarbamazine. |
| ***Wuchereria bancrofti, Brugia malayi*** | Lymphatic filariasis (elephantiasis)—worms invade lymph nodes. → inflammation → lymphedema E; symptom onset after 9 mo–1 yr. | Female mosquito. | Diethylcarbamazine. |

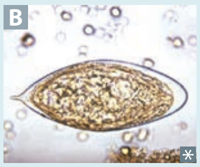
## Cestodes (tapeworms)

| ORGANISM | DISEASE | TRANSMISSION | TREATMENT |
|---|---|---|---|
| ***Taenia solium*** **A** | Intestinal tapeworm | Ingestion of larvae encysted in undercooked pork | Praziquantel |
| | Cysticercosis, neurocysticercosis (cystic CNS lesions, seizures) B | Ingestion of eggs in food contaminated with human feces | Praziquantel; albendazole for neurocysticercosis |
| ***Diphyllobothrium latum*** | Vitamin $B_{12}$ deficiency (tapeworm competes for $B_{12}$ in intestine) → megaloblastic anemia | Ingestion of larvae in raw freshwater fish | Praziquantel, niclosamide |
| ***Echinococcus granulosus*** **C** | Hydatid cysts D ("eggshell calcification") in liver E; cyst rupture can cause anaphylaxis | Ingestion of eggs in food contaminated with dog feces<br>Sheep are an intermediate host | Albendazole; surgery for complicated cysts |

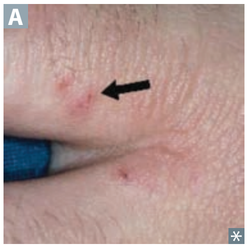
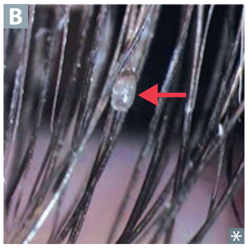




## Trematodes (flukes)

| ORGANISM | DISEASE | TRANSMISSION | TREATMENT |
|---|---|---|---|
| ***Schistosoma***   | Liver and spleen enlargement (A shows *S mansoni* egg with lateral spine), fibrosis, inflammation, portal hypertension<br>Chronic infection with *S haematobium* (egg with terminal spine B) can lead to squamous cell carcinoma of the bladder (painless hematuria) and pulmonary hypertension | Snails are intermediate host; cercariae penetrate skin of humans in contact with contaminated fresh water (eg, swimming or bathing) | Praziquantel |
| ***Clonorchis sinensis*** | Biliary tract inflammation → pigmented gallstones<br>Associated with cholangiocarcinoma | Undercooked fish | Praziquantel |

## Ectoparasites

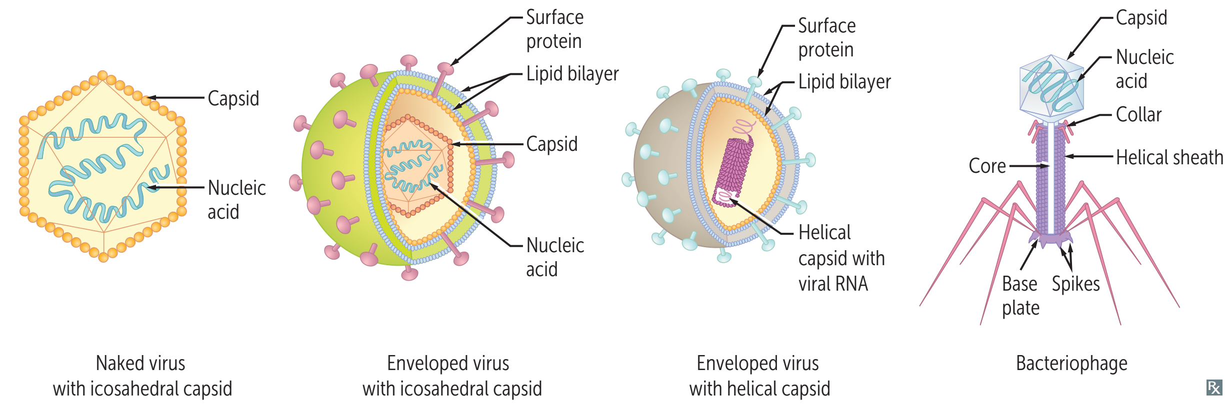
| | | |
|---|---|---|
| ***Sarcoptes scabiei***  | Mites burrow into stratum corneum and cause **scabies**—pruritus (worse at night) and serpiginous burrows (lines) often between fingers and toes A. | Common in children, crowded populations (jails, nursing homes); transmission through skin-to-skin contact (most common) or via fomites. Treatment: permethrin cream, oral ivermectin, washing/drying all clothing/bedding, treat close contacts. |
| ***Pediculus humanus/ Phthirus pubis***  | Blood-sucking lice that cause intense pruritus with associated excoriations, commonly on scalp and neck (head lice), waistband and axilla (body lice), or pubic and perianal regions (pubic lice). | Body lice can transmit *Rickettsia prowazekii* (epidemic typhus), *Borrelia recurrentis* (relapsing fever), *Bartonella quintana* (trench fever). Treatment: pyrethroids, malathion, or ivermectin lotion, and nit B combing. Children with head lice can be treated at home without interrupting school attendance. |

## Parasite hints

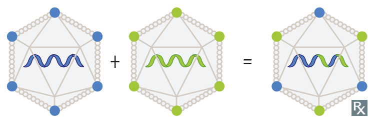
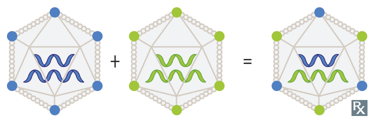
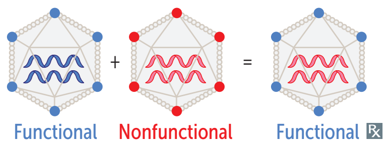
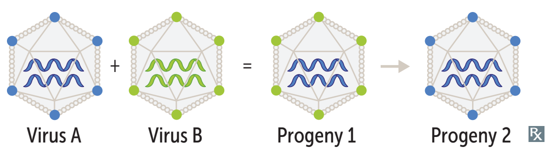
| ASSOCIATIONS | ORGANISM |
|---|---|
| Biliary tract disease, cholangiocarcinoma | *Clonorchis sinensis* |
| Brain cysts, seizures | *Taenia solium* (neurocysticercosis) |
| Hematuria, squamous cell bladder cancer | *Schistosoma haematobium* |
| Liver (hydatid) cysts, exposure to infected dogs | *Echinococcus granulosus* |
| Iron deficiency anemia | *Ancylostoma*, *Necator* |
| Myalgias, periorbital edema | *Trichinella spiralis* |
| Nocturnal perianal pruritus | *Enterobius* |
| Portal hypertension | *Schistosoma mansoni*, *Schistosoma japonicum* |
| Vitamin $B_{12}$ deficiency | *Diphyllobothrium latum* |

## ▸ MICROBIOLOGY—VIROLOGY

### Viral structure—general features




### Viral genetics

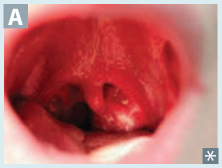
| | | |
|---|---|---|
| **Recombination** | Exchange of genes between 2 chromosomes by crossing over within regions of significant base sequence homology. |  |
| **Reassortment** | When viruses with segmented genomes (eg, influenza virus) exchange genetic material. For example, the 2009 novel H1N1 influenza A pandemic emerged via complex viral reassortment of genes from human, swine, and avian viruses. Has potential to cause antigenic shift. |  |
| **Complementation** | When 1 of 2 viruses that infect the cell has a mutation that results in a nonfunctional protein, the nonmutated virus "complements" the mutated one by making a functional protein that serves both viruses. For example, hepatitis D virus requires the presence of replicating hepatitis B virus to supply HBsAg, the envelope protein for HDV. |   |
| **Phenotypic mixing** | Occurs with simultaneous infection of a cell with 2 viruses. For progeny 1, genome of virus A can be partially or completely coated (forming pseudovirion) with the surface proteins of virus B. Type B protein coat determines the tropism (infectivity) of the hybrid virus. Progeny from subsequent infection of a cell by progeny 1 will have a type A coat that is encoded by its type A genetic material. |   |

| | | |
|---|---|---|
| **DNA viral genomes** | All DNA viruses have dsDNA genomes except Parvoviridae (ssDNA).<br>All are linear except papilloma-, polyoma-, and hepadnaviruses (circular). | All are dsDNA (like our cells), except "**part-of-a-virus**" (**parvovirus**) is ssDNA.<br>*Parvus* = small. |
| **RNA viral genomes** | All RNA viruses have ssRNA genomes except Reoviridae (dsRNA).<br>⊕ stranded RNA viruses: I went to a **retro** (**retro**virus) **toga** (**toga**virus) party, where I drank **flav**ored (**flav**ivirus) **Corona** (**corona**virus) and ate **hippie** (**hepe**virus) **Cali**fornia (**cali**civirus) **pic**kles (**pic**ornavirus). | All are ssRNA, except "**re**peat**o**-virus" (**reo**virus) is dsRNA. |
| **Naked viral genome infectivity** | Purified nucleic acids of most dsDNA viruses (except poxviruses and HBV) and ⊕ strand ssRNA (≈ mRNA) viruses are infectious. Naked nucleic acids of ⊖ strand ssRNA and dsRNA viruses are not infectious. They require polymerases contained in the complete virion. | |
| **Viral envelopes** | Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions include herpesviruses, which acquire envelopes from nuclear membrane.<br>Naked (nonenveloped) viruses include papillomavirus, adenovirus, parvovirus, polyomavirus, calicivirus, picornavirus, reovirus, and hepevirus. | Enveloped DNA viruses (**h**erpesvirus, **h**epadnavirus, **p**oxvirus) **h**ave **h**elpful **p**rotection. |
| **DNA virus characteristics** | Some general rules—all DNA viruses: | |

| GENERAL RULE | COMMENTS |
|---|---|
| Are **HHAPPPP**y viruses | **H**epadna, **H**erpes, **A**deno, **P**ox, **P**arvo, **P**apilloma, **P**olyoma. |
| Are double stranded | Except parvo (single stranded). |
| Have linear genomes | Except papilloma and polyoma (circular, supercoiled) and hepadna (circular, incomplete). |
| Are icosahedral | Except pox (complex). |
| Replicate in the nucleus | Except pox (carries own DNA-dependent RNA polymerase). |

## DNA viruses

All replicate in the nucleus (except poxvirus). "**Pox** is out of the **box** (nucleus)."

| VIRAL FAMILY | ENVELOPE | DNA STRUCTURE | MEDICAL IMPORTANCE |
|---|---|---|---|
| **Herpesviruses** | Yes | DS and linear | See Herpesviruses entry |
| **Poxvirus** | Yes | DS and linear (largest DNA virus) | Smallpox eradicated world wide by use of the live-attenuated vaccine<br>Cowpox ("milkmaid blisters")<br>**Molluscum contagiosum**—flesh-colored papule with central umbilication |
| **Hepadnavirus** | Yes | Partially DS and circular | HBV:<br>▪ Acute or chronic hepatitis<br>▪ Not a retrovirus but has reverse transcriptase |
| **Adenovirus**<br>A  | No | DS and linear | Febrile pharyngitis A—sore throat<br>Acute hemorrhagic cystitis<br>Pneumonia<br>Conjunctivitis—"pink eye"<br>Gastroenteritis<br>Myocarditis |
| **Papillomavirus** | No | DS and circular | HPV—warts, cancer (cervical, anal, penile, or oropharyngeal); serotypes 1, 2, 6, 11 associated with warts; serotypes 16, 18 associated with cancer |
| **Polyomavirus** | No | DS and circular | JC virus—progressive multifocal leukoencephalopathy (PML) in HIV<br>BK virus—transplant patients, commonly targets kidney<br>**JC**: **J**unky **C**erebrum; **BK**: **B**ad **K**idney |
| **Parvovirus** | No | SS and linear (smallest DNA virus) | B19 virus—aplastic crises in sickle cell disease, "slapped cheek" rash in children (erythema infectiosum, or fifth disease); infects RBC precursors and endothelial cells → RBC destruction → hydrops fetalis and death in fetus, pure RBC aplasia and rheumatoid arthritis–like symptoms in adults |

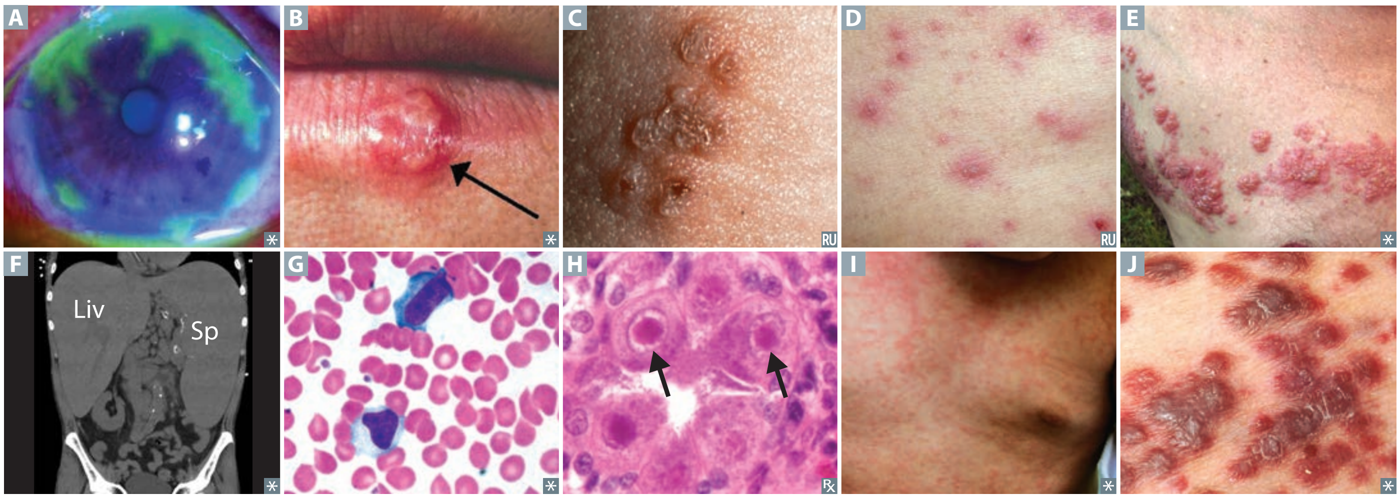
## Herpesviruses

Enveloped, DS, and linear viruses

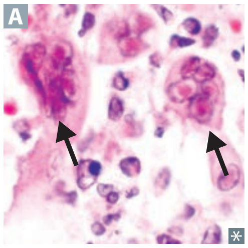
| VIRUS | ROUTE OF TRANSMISSION | CLINICAL SIGNIFICANCE | NOTES |
|---|---|---|---|
| **Herpes simplex virus-1** | Respiratory secretions, saliva | Gingivostomatitis, keratoconjunctivitis A, herpes labialis (cold sores) B, herpetic whitlow on finger, temporal lobe encephalitis, esophagitis, erythema multiforme | Most commonly latent in trigeminal ganglia<br>Most common cause of sporadic encephalitis, can present as altered mental status, seizures, and/or aphasia |
| **Herpes simplex virus-2** | Sexual contact, perinatal | Herpes genitalis C, neonatal herpes | Most commonly latent in sacral ganglia<br>Viral meningitis more common with HSV-2 than with HSV-1 |

### Herpesviruses *(continued)*

| VIRUS | ROUTE OF TRANSMISSION | CLINICAL SIGNIFICANCE | NOTES |
|---|---|---|---|
| **Varicella-Zoster virus (HHV-3)** | Respiratory secretions, contact with fluid from vesicles | Varicella-zoster (chickenpox D, shingles E), encephalitis, pneumonia<br>Most common complication of shingles is post-herpetic neuralgia | Latent in dorsal root or trigeminal ganglia; CN $V_1$ branch involvement can cause herpes zoster ophthalmicus |
| **Epstein-Barr virus (HHV-4)** | Respiratory secretions, saliva; aka "kissing disease," (common in teens, young adults) | **Mononucleosis**—fever, hepatosplenomegaly F, pharyngitis, and lymphadenopathy (especially posterior cervical nodes); avoid contact sports until resolution due to risk of splenic rupture<br>Associated with lymphomas (eg, endemic Burkitt lymphoma), nasopharyngeal carcinoma (especially Asian adults), lymphoproliferative disease in transplant patients | Infects **B** cells through CD**21**, "Must be **21** to drink **B**eer in a **Barr**"<br>Atypical lymphocytes on peripheral blood smear G—not infected B cells but reactive cytotoxic T cells<br>⊕ Monospot test—heterophile antibodies detected by agglutination of sheep or horse RBCs<br>Use of amoxicillin (eg, for presumed strep pharyngitis) can cause maculopapular rash |
| **Cytomegalo-virus (HHV-5)** | Congenital, transfusion, sexual contact, saliva, urine, transplant | Mononucleosis (⊖ Monospot) in immunocompetent patients; infection in immunocompromised, especially pneumonia in transplant patients; esophagitis; AIDS **retinitis** ("**sight**omegalovirus"): hemorrhage, cotton-wool exudates, vision loss<br>Congenital CMV | Infected cells have characteristic "owl eye" intranuclear inclusions H<br>Latent in mononuclear cells |
| **Human herpes-viruses 6 and 7** | Saliva | Roseola infantum (exanthem subitum): high fevers for several days that can cause seizures, followed by diffuse macular rash (starts on trunk then spreads to extremities) I; usually seen in children $<2$ years old | **Roseola**: fever first, **Ros**y (rash) **la**ter<br>Self-limited illness<br>HHV-7—less common cause of roseola |
| **Human herpesvirus 8** | Sexual contact | Kaposi sarcoma (neoplasm of endothelial cells). Seen in HIV/AIDS and transplant patients. Dark/violaceous plaques or nodules J representing vascular proliferations | Can also affect GI tract and lungs |



## HSV identification



PCR of skin lesions is test of choice.
CSF PCR for herpes encephalitis.
Tzanck test (outdated)—a smear of an opened skin vesicle to detect multinucleated giant cells A commonly seen in HSV-1, HSV-2, and VZV infection.
Intranuclear eosinophilic Cowdry A inclusions also seen with HSV-1, HSV-2, VZV.

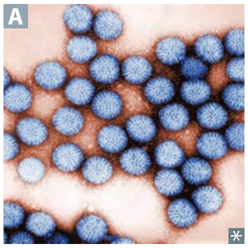
## Receptors used by viruses

| VIRUS | RECEPTORS |
|---|---|
| CMV | Integrins (heparan sulfate) |
| EBV | CD21 |
| HIV | CD4, CXCR4, CCR5 |
| **P**arvovirus B19 | **P** antigen on RBCs |
| **Rhino**virus | **ICAM**-1 (**I CAM**e to see the **rhino**) |

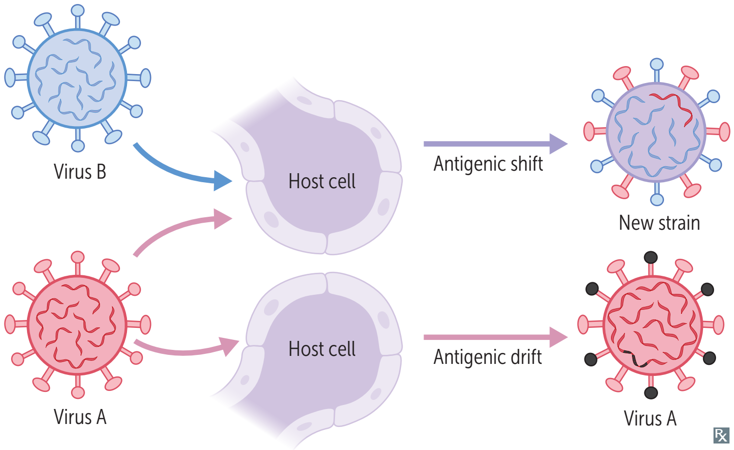
**RNA viruses** All replicate in the cytoplasm (except retrovirus and influenza virus). "Retro flu is outta cyt (sight)."

| VIRAL FAMILY | ENVELOPE | RNA STRUCTURE | CAPSID SYMMETRY | MEDICAL IMPORTANCE |
|---|---|---|---|---|
| **Reoviruses** | No | DS linear<br>Multisegmented | Icosahedral (double) | Coltivirus[a]—Colorado tick fever<br>Rotavirus—cause of fatal diarrhea in children |
| **Picornaviruses** | No | SS ⊕ linear | Icosahedral | Poliovirus—polio-Salk/Sabin vaccines—IPV/OPV<br>Echovirus—aseptic meningitis<br>Rhinovirus—"common cold"<br>Coxsackievirus—aseptic meningitis; herpangina (mouth blisters, fever); hand, foot, and mouth disease; myocarditis; pericarditis<br>HAV—acute viral hepatitis PERCH |
| **Hepevirus** | No | SS ⊕ linear | Icosahedral | HEV |
| **Caliciviruses** | No | SS ⊕ linear | Icosahedral | Norovirus—viral gastroenteritis |
| **Flaviviruses** | Yes | SS ⊕ linear | Icosahedral | HCV<br>Yellow fever[a]<br>Dengue[a]<br>St. Louis encephalitis[a]<br>West Nile virus[a]—meningoencephalitis, flaccid paralysis<br>Zika virus[a] |
| **Togaviruses** | Yes | SS ⊕ linear | Icosahedral | Toga CREW—Chikungunya virus[a] (co-infection with dengue virus can occur), Rubella, Eastern and Western equine encephalitis |
| **Retroviruses** | Yes | SS ⊕ linear<br>2 copies | Icosahedral (HTLV), complex and conical (HIV) | Have reverse transcriptase<br>HTLV—T-cell leukemia<br>HIV—AIDS |
| **Coronaviruses** | Yes | SS ⊕ linear | Helical | "Common cold," SARS, MERS, COVID-19 |
| **Orthomyxoviruses** | Yes | SS ⊖ linear<br>8 segments | Helical | Influenza virus |
| **Paramyxoviruses** | Yes | SS ⊖ linear<br>Nonsegmented | Helical | PaRaMyxovirus:<br>Parainfluenza—croup<br>RSV—bronchiolitis in babies<br>Measles, Mumps |
| **Rhabdoviruses** | Yes | SS ⊖ linear | Helical | Rabies |
| **Filoviruses** | Yes | SS ⊖ linear | Helical | Ebola/Marburg hemorrhagic fever—often fatal. |
| **Arenaviruses** | Yes | SS ⊕ and ⊖ circular<br>2 segments | Helical | LCMV—lymphocytic choriomeningitis virus<br>Lassa fever encephalitis—spread by rodents |
| **Bunyaviruses** | Yes | SS ⊖ circular<br>3 segments | Helical | California encephalitis[a]<br>Sandfly/Rift Valley fevers[a]<br>Crimean-Congo hemorrhagic fever[a]<br>Hantavirus—hemorrhagic fever, pneumonia |
| **Delta virus** | Yes | SS ⊖ circular | Uncertain | HDV is a "Defective" virus that requires the presence of HBV to replicate |

SS, single-stranded; DS, double-stranded; ⊕, positive sense; ⊖, negative sense; [a]= arbovirus, arthropod borne (mosquitoes, ticks).

| | | |
|---|---|---|
| **Negative-stranded viruses** | Must transcribe ⊖ strand to ⊕. Virion brings its own RNA-dependent RNA polymerase. They include **a**renaviruses, **b**unyaviruses, **p**aramyxoviruses, **o**rthomyxoviruses, **f**iloviruses, and **r**habdoviruses. | **A**lways **b**ring **p**olymerase **o**r **f**ail **r**eplication. |
| **Segmented viruses** | All are RNA viruses. They include **B**unyaviruses (**3** segments), **O**rthomyxoviruses (influenza viruses) (**8** segments), **A**renaviruses (**2** segments), and **R**eoviruses (**10–12** segments). | **BOAR**ding flight **382** in **10–12** minutes. |
| **Picornavirus** | Includes **P**oliovirus, **E**chovirus, **R**hinovirus, **C**oxsackievirus, and **H**AV. RNA is translated into 1 large polypeptide that is cleaved by virus-encoded proteases into functional viral proteins. Poliovirus, echovirus, and coxsackievirus are enteroviruses and can cause aseptic (viral) meningitis. | Pico**RNA**virus = small **RNA** virus. **PERCH** on a "**peak**" (**pic**o). |
| **Rhinovirus** | A picornavirus. Nonenveloped RNA virus. Cause of common cold; > 100 serologic types. Acid labile—destroyed by stomach acid; therefore, does not infect the GI tract (unlike the other picornaviruses). | **Rhino** has a runny **nose**. |
| **Rotavirus**  | Segmented dsRNA virus (a reovirus) A. Most important global cause of infantile gastroenteritis. Major cause of acute diarrhea in the United States during winter, especially in day care centers, kindergartens. Villous destruction with atrophy leads to ↓ absorption of $Na^+$ and loss of $K^+$. | **Rota**virus = **r**ight **o**ut **t**he **a**nus. CDC recommends routine vaccination of all infants except those with a history of intussusception (rare adverse effect of rotavirus vaccination) or SCID. |

| | | |
|---|---|---|
| **Influenza viruses** | Orthomyxoviruses. Enveloped, ⊖ ssRNA viruses with segmented genome. Contain hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Patients at risk for fatal bacterial superinfection, most commonly *S aureus*, *S pneumoniae*, and *H influenzae*.<br>Treatment: supportive +/– neuraminidase inhibitor (eg, oseltamivir, zanamivir). | Hemagglutin**in**: lets the virus **in**<br>Neuraminid**away**s: sends the virus **away**<br>Reformulated vaccine ("the flu shot") contains viral strains most likely to appear during the flu season, due to the virus' rapid genetic change.<br>Killed viral vaccine is most frequently used.<br>Live attenuated vaccine contains temperature-sensitive mutant that replicates in the nose but not in the lung; administered intranasally.<br>**S**udden **s**hift is more deadly than gra**d**ual **d**rift. |
| **Genetic/antigenic shift** | Infection of 1 cell by 2 different segmented viruses (eg, swine influenza and human influenza viruses) → RNA segment reassortment → dramatically different virus (genetic shift) → major global outbreaks (pandemics). | |
| **Genetic/antigenic drift** | Random mutation in hemagglutinin (HA) or neuraminidase (NA) genes → minor changes in HA or NA protein (drift) occur frequently → major global outbreaks (pandemics). | |



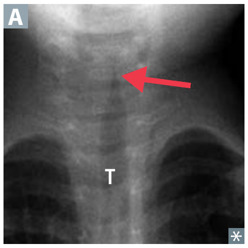

**Rubella virus**


A togavirus. Causes rubella, once known as German (3-day) measles. Fever, postauricular and other lymphadenopathy, arthralgias, and fine, maculopapular rash that starts on face and spreads centrifugally to involve trunk and extremities A.
Causes mild disease in children but serious congenital disease (a TORCH infection). Congenital rubella findings include classic triad of sensorineural deafness, cataracts, and patent ductus arteriosus. "Blueberry muffin" appearance may be seen due to dermal extramedullary hematopoiesis.

**Paramyxoviruses**

Paramyxoviruses cause disease in children. They include those that cause parainfluenza (croup), mumps, measles, RSV, and human metapneumovirus. All subtypes can cause respiratory tract infection (bronchiolitis, pneumonia) in infants. All contain surface F (fusion) protein, which causes respiratory epithelial cells to fuse and form multinucleated cells. Palivizumab (monoclonal antibody against F protein) prevents pneumonia caused by RSV infection in premature infants.
**P**alivizumab for **p**aramyxovirus (RSV) **p**rophylaxis in **p**reemies.

### Acute laryngotracheobronchitis




Also called croup. Caused by parainfluenza viruses. Virus membrane contains hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Results in a "seal-like" barking cough and inspiratory stridor. Narrowing of upper trachea and subglottis leads to characteristic steeple sign on x-ray A.

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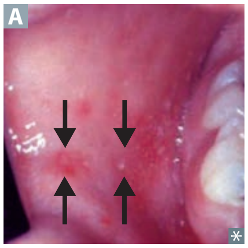
### Measles (rubeola) virus





Usual presentation involves prodromal fever with cough, coryza, and conjunctivitis, then eventually Koplik spots (bright red spots with blue-white center on buccal mucosa A), followed 1–2 days later by a maculopapular rash B that starts at the head/neck and spreads downward.

Lymphadenitis with Warthin-Finkeldey giant cells (fused lymphocytes) in a background of paracortical hyperplasia. Possible sequelae:

- Subacute sclerosing panencephalitis (SSPE): personality changes, dementia, autonomic dysfunction, death (occurs years later)
- Encephalitis (1:1000): symptoms appear within few days of rash
- Giant cell pneumonia (rare except in immunosuppressed)

4 C's of measles:
- Cough
- Coryza
- Conjunctivitis
- "C"oplik spots

Vitamin A supplementation can reduce morbidity and mortality from measles, particularly in malnourished children.

Pneumonia is the most common cause of measles-associated death in children.

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### Mumps virus


Uncommon due to effectiveness of MMR vaccine.

Symptoms: **P**arotitis A, **O**rchitis (inflammation of testes), aseptic **M**eningitis, and **P**ancreatitis. Can cause sterility (especially after puberty).

Mumps makes your parotid glands and testes as big as **POM-P**oms.

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### Chikungunya virus

An alphavirus member of togavirus family, transmitted by *Aedes* mosquito. Systemic infection that produces inflammatory polyarthritis that can become chronic. Other symptoms include high fever, maculopapular rash, headache, lymphadenopathy. Hemorrhagic manifestations are uncommon (vs dengue fever). Diagnosed with RT-PCR or serology. No antiviral therapy and no vaccine.

---

### Dengue virus

A flavivirus, transmitted by *Aedes* mosquito; most common mosquito-borne viral disease in the world. Can present as dengue fever (fever, rash, headache, myalgias, arthralgias, neutropenia), dengue hemorrhagic fever (dengue fever + bleeding and plasma leakage due to thrombocytopenia and extremely high or low hematocrit), or dengue shock syndrome (plasma leakage leading to circulatory collapse). Diagnosed by PCR or serology.

Dengue hemorrhagic fever is most common in patients infected with a different serotype after their initial infection due to antibody-dependent enhancement of disease.

Presents similarly to Chikungunya virus and is transmitted by the same mosquito vector; coinfections can occur. Dengue virus is more likely to cause neutropenia, thrombocytopenia, hemorrhage, shock, and death.

Live, recombinant vaccine uses yellow fever virus as a backbone into which the genes for the envelope and premembrane proteins of dengue virus have been inserted.

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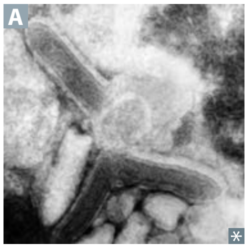
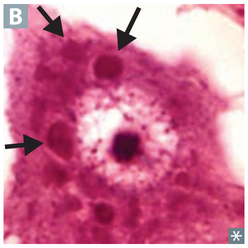
### Rabies virus




Bullet-shaped virus A. Negri bodies (cytoplasmic inclusions B) commonly found in Purkinje cells of cerebellum and in hippocampal neurons. Rabies has long incubation period (weeks to months) before symptom onset. Postexposure prophylaxis is wound cleaning plus immunization with killed vaccine and rabies immunoglobulin. Example of passive-active immunity.

Travels to the CNS by migrating in a retrograde fashion (via dynein motors) up nerve axons after binding to ACh receptors.

Progression of disease: fever, malaise → agitation, photophobia, hydrophobia, hypersalivation → paralysis, coma → death.

Infection more commonly from bat, raccoon, and skunk bites than from dog bites in the United States; aerosol transmission (eg, bat caves) also possible.

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### Yellow fever virus

A flavivirus (also an arbovirus) transmitted by *Aedes* mosquitoes. Virus has a monkey or human reservoir.

Symptoms: high fever, black vomitus, jaundice, hemorrhage, backache. May see Councilman bodies (eosinophilic apoptotic globules) on liver biopsy.

*Flavi* = yellow, jaundice.

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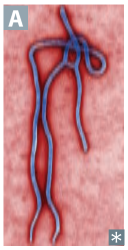
### Ebola virus




A filovirus A. Following an incubation period of up to 21 days, presents with abrupt onset of flu-like symptoms, diarrhea/vomiting, high fever, myalgia. Can progress to DIC, diffuse hemorrhage, shock.

Diagnosed with RT-PCR within 48 hr of symptom onset. High mortality rate.

Transmission requires direct contact with bodily fluids, fomites (including dead bodies), infected bats or primates (apes/monkeys); high incidence of nosocomial infection.

Supportive care, no definitive treatment. Vaccination of contacts, strict isolation of infected individuals, and barrier practices for health care workers are key to preventing transmission.

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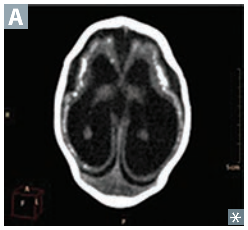
### Zika virus




A flavivirus most commonly transmitted by *Aedes* mosquito bites.

Causes conjunctivitis, low-grade pyrexia, and itchy rash in 20% of cases. Outbreaks more common in tropical and subtropical climates. Supportive care, no definitive treatment.

Diagnose with RT-PCR or serology.

Sexual and vertical transmission occurs.

Can lead to miscarriage or congenital Zika syndrome: brain imaging A shows ventriculomegaly, subcortical calcifications. Clinical features include:

- Microcephaly
- Ocular anomalies
- Motor abnormalities (spasticity, seizures)

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### Severe acute respiratory syndrome coronavirus 2

SARS-CoV-2 is a novel ⊕ ssRNA coronavirus and the cause of the ongoing COVID-19 pandemic. Spreads primarily through respiratory droplets and aerosols. Host cell entry occurs by attachment of viral spike protein to angiotensin-converting enzyme 2 receptor on cell membranes.

Clinical course varies; often asymptomatic. Symptoms include

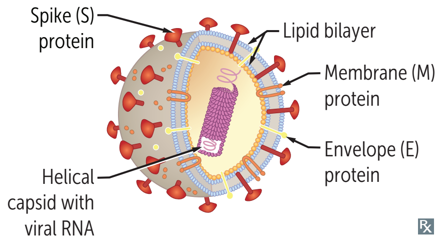
- Common: fever, dry cough, shortness of breath, fatigue.
- More specific: anosmia (loss of smell), dysgeusia (altered taste).

Potential complications include respiratory failure, hypercoagulability, shock, organ failure, death.

Risk factors for severe illness or death include increasing age, obesity, diabetes, hypertension, chronic kidney disease, and severe cardiopulmonary illness.

Diagnosed by RT-PCR (most common); antigen and antibody tests are available.

Treatment options for hospitalized adults include remdesivir (nucleoside analog), convalescent plasma, and dexamethasone (to treat cytokine release syndrome).

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**Hepatitis viruses**

Signs and symptoms of all hepatitis viruses: episodes of fever, jaundice, ↑ ALT and AST. Naked viruses (HAV and HEV) lack an envelope and are not destroyed by the gut: the vowels hit your bowels.

HBV DNA polymerase has DNA- and RNA-dependent activities. Upon entry into nucleus, the polymerase completes the partial dsDNA. Host RNA polymerase transcribes mRNA from viral DNA to make viral proteins. The DNA polymerase then reverse transcribes viral RNA to DNA, which is the genome of the progeny virus.

HCV lacks 3′-5′ exonuclease activity → no proofreading ability → antigenic variation of HCV envelope proteins. Host antibody production lags behind production of new mutant strains of HCV.

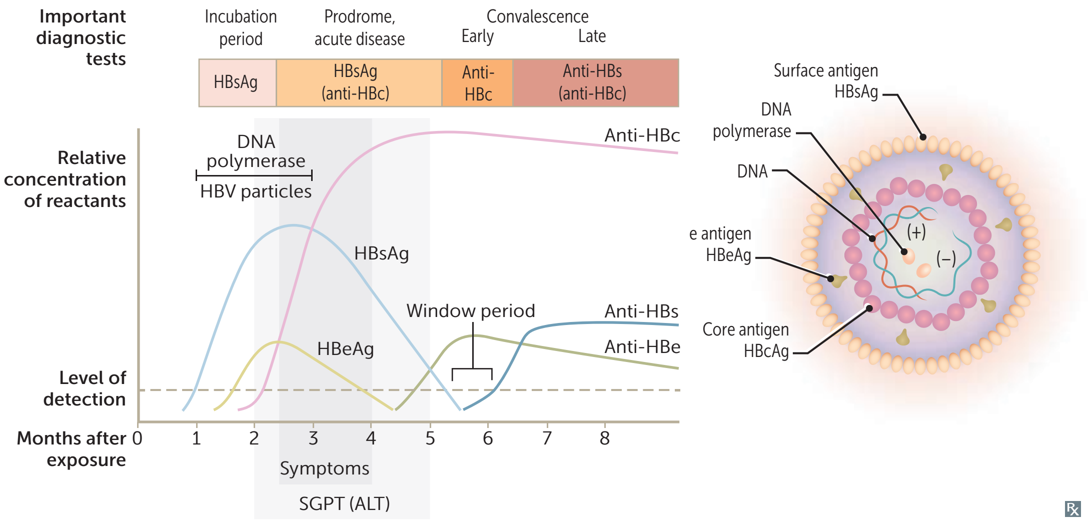
| Virus | HAV | HBV | HCV | HDV | HEV |
|---|---|---|---|---|---|
| FAMILY | RNA picornavirus | DNA hepadnavirus | RNA flavivirus | RNA deltavirus | RNA hepevirus |
| TRANSMISSION | Fecal-oral (shellfish, travelers, day care) | Parenteral (Blood), sexual (Bedroom), perinatal (Birthing) | Primarily blood (IV drugs, posttransfusion) | Parenteral, sexual, perinatal | Fecal-oral, especially waterborne |
| INCUBATION | Short (weeks) | Long (months) | Long | Superinfection (HDV after HBV) = short<br>Coinfection (HDV with HBV) = long | Short |
| CLINICAL COURSE | Acute and self limiting (adults), Asymptomatic (children) | Initially like serum sickness (fever, arthralgias, rash); may progress to carcinoma | May progress to Cirrhosis or Carcinoma | Similar to HBV | Fulminant hepatitis in Expectant (pregnant) patients |
| PROGNOSIS | Good | Adults → mostly full resolution; neonates → worse prognosis | Majority develop stable, Chronic hepatitis C | Superinfection → worse prognosis | High mortality in pregnant patients |
| HCC RISK | No | Yes | Yes | Yes | No |
| LIVER BIOPSY | Hepatocyte swelling, monocyte infiltration, Councilman bodies | Granular eosinophilic "ground glass" appearance due to accumulation of surface antigen within infected hepatocytes; cytotoxic T cells mediate damage | Lymphoid aggregates with focal areas of macrovesicular steatosis | Similar to HBV | Patchy necrosis |
| NOTES | No carrier state | Carrier state common | Carrier state very common | Defective virus, Depends on HBV HBsAg coat for entry into hepatocytes | Enteric, Epidemic (eg, in parts of Asia, Africa, Middle East), no carrier state |

### Extrahepatic manifestations of hepatitis B and C

| | Hepatitis B | Hepatitis C |
|---|---|---|
| HEMATOLOGIC | Aplastic anemia | Essential mixed cryoglobulinemia, ↑ risk B-cell NHL, ITP, autoimmune hemolytic anemia |
| RENAL | Membranous GN > membranoproliferative GN | Membranoproliferative GN > membranous GN |
| VASCULAR | Polyarteritis nodosa | Leukocytoclastic vasculitis |
| DERMATOLOGIC | | Sporadic porphyria cutanea tarda, lichen planus |
| ENDOCRINE | | ↑ risk of diabetes mellitus, autoimmune hypothyroidism |

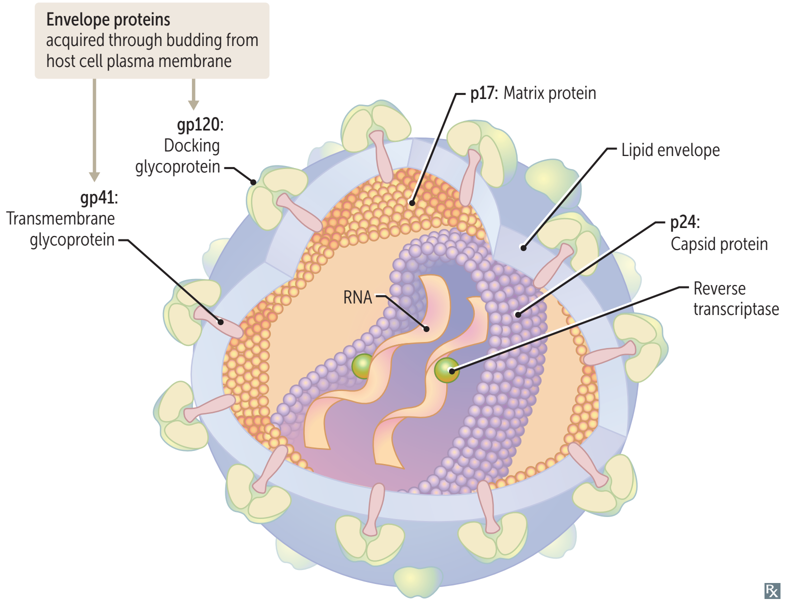
### Hepatitis serologic markers

| | |
|---|---|
| **Anti-HAV (IgM)** | IgM antibody to HAV; best test to detect acute hepatitis A. |
| **Anti-HAV (IgG)** | IgG antibody indicates prior HAV infection and/or prior vaccination; protects against reinfection. |
| **HBsAg** | Antigen found on surface of HBV; indicates hepatitis B infection. |
| **Anti-HBs** | Antibody to HBsAg; indicates immunity to hepatitis B due to vaccination or recovery from infection. |
| **HBcAg** | Antigen associated with core of HBV. |
| **Anti-HBc** | Antibody to HBcAg; IgM = acute/recent infection; IgG = prior exposure or chronic infection. IgM anti-HBc may be the sole ⊕ marker of infection during window period. |
| **HBeAg** | Secreted by infected hepatocyte into circulation. Not part of mature HBV virion. Indicates active viral replication and therefore high transmissibility and poorer prognosis. |
| **Anti-HBe** | Antibody to HBeAg; indicates low transmissibility. |




| | HBsAg | Anti-HBs | HBeAg | Anti-HBe | Anti-HBc |
|---|---|---|---|---|---|
| Acute HBV | ✓ | | ✓ | | IgM |
| Window | | | | ✓ | IgM |
| Chronic HBV (high infectivity) | ✓ | | ✓ | | IgG |
| Chronic HBV (low infectivity) | ✓ | | | ✓ | IgG |
| Recovery | | ✓ | | ✓ | IgG |
| Immunized | | ✓ | | | |

## HIV




Diploid genome (2 molecules of RNA).

The 3 structural genes (protein coded for):

- *env* (gp120 and gp41):
  - Formed from cleavage of gp160 to form envelope glycoproteins.
  - gp120—attachment to host CD4+ T cell.
  - gp41—fusion and entry.
- *gag* (p24 and p17)—capsid and matrix proteins, respectively.
- ***pol***—**R**everse transcriptase, **I**ntegrase, **P**rotease; **RIP** "**Pol**" (Paul)

Reverse transcriptase synthesizes dsDNA from genomic RNA; dsDNA integrates into host genome.

Virus binds CD4 as well as a coreceptor, either CCR5 on macrophages (early infection) or CXCR4 on T cells (late infection).

Homozygous CCR5 mutation = immunity.

Heterozygous CCR5 mutation = slower course.

## HIV diagnosis

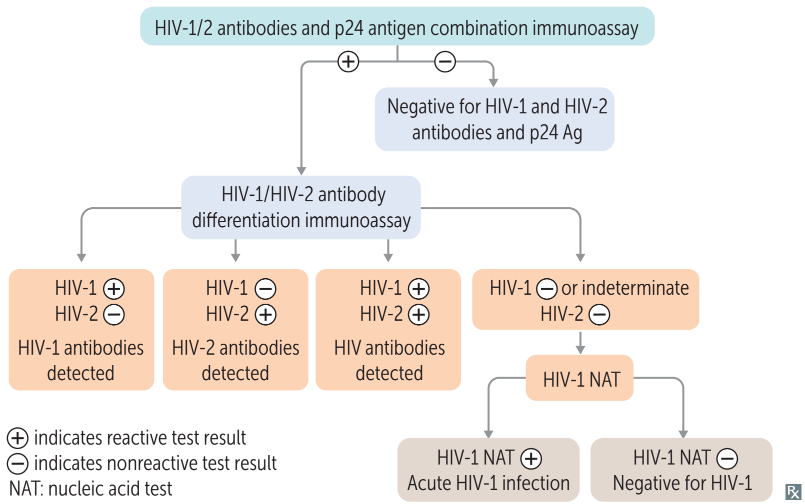
Diagnosis made with HIV-1/2 Ag/Ab immunoassays. These immunoassays detect viral p24 Ag capsid protein and IgG Abs to HIV-1/2. Very high sensitivity/specificity.

Viral load tests determine the amount of viral RNA in the plasma. Use viral load to monitor effect of drug therapy. Use HIV genotyping to determine appropriate therapy.

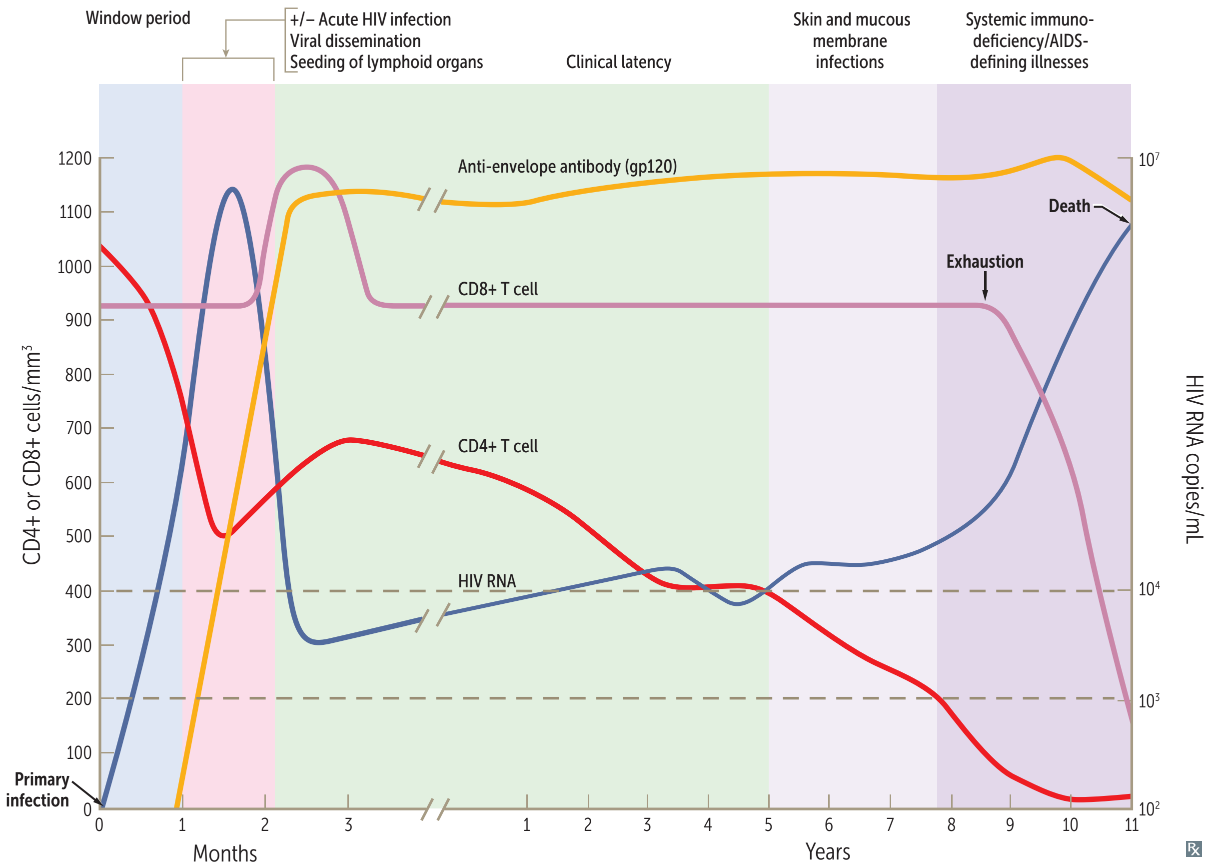
AIDS diagnosis: ≤ 200 CD4+ cells/$mm^3$ (normal: 500–1500 cells/$mm^3$) or HIV ⊕ with AIDS-defining condition (eg, *Pneumocystis* pneumonia).

Western blot tests are no longer recommended by the CDC for confirmatory testing.

HIV-1/2 Ag/Ab testing is not recommended in babies with suspected HIV due to maternally transferred antibody. Use HIV viral load instead.



### Time course of untreated HIV infection




Dashed lines on CD4+ cell count axis indicate moderate immunocompromise (< 400 CD4+ cells/mm$^3$) and when AIDS-defining illnesses emerge (< 200 CD4+ cells/mm$^3$).

Most patients who do not receive treatment eventually die of complications of HIV infection.

Four stages of untreated infection:
1. Flu-like (acute)
2. Feeling fine (latent)
3. Falling count
4. Final crisis

During clinical latency phase, virus replicates in lymph nodes

**Common diseases of HIV-positive adults**

↓ CD4+ cell count → reactivation of past infections (eg, TB, HSV, shingles), dissemination of bacterial infections and fungal infections (eg, coccidioidomycosis), and non-Hodgkin lymphomas.

| PATHOGEN | PRESENTATION | FINDINGS |
|---|---|---|
| **CD4+ cell count < 500/mm$^3$** | | |
| *Candida albicans* | Oral thrush | Scrapable white plaque, pseudohyphae on microscopy |
| EBV | Oral hairy leukoplakia | Unscrapable white plaque on lateral tongue |
| HHV-8 | Kaposi sarcoma | Perivascular spindle cells invading and forming vascular tumors on histology |
| HPV | Squamous cell carcinoma at site(s) of sexual contact (most commonly anus, cervix, oropharynx) | |
| **CD4+ cell count < 200/mm$^3$** | | |
| *Histoplasma capsulatum* | Fever, weight loss, fatigue, cough, dyspnea, nausea, vomiting, diarrhea | Oval yeast cells within macrophages |
| HIV | Dementia | Cerebral atrophy on neuroimaging |
| JC virus (reactivation) | Progressive multifocal leukoencephalopathy | Nonenhancing areas of demyelination on MRI |
| *Pneumocystis jirovecii* | *Pneumocystis* pneumonia | "Ground-glass" opacities on chest imaging |
| **CD4+ cell count < 100/mm$^3$** | | |
| *Aspergillus fumigatus* | Hemoptysis, pleuritic pain | Cavitation or infiltrates on chest imaging |
| *Bartonella* spp | Bacillary angiomatosis | Multiple red to purple papules or nodules<br>Biopsy with neutrophilic inflammation |
| *Candida albicans* | Esophagitis | White plaques on endoscopy; yeast and pseudohyphae on biopsy |
| CMV | **C**olitis, **R**etinitis, **E**sophagitis, **E**ncephalitis, **P**neumonitis (**CREEP**) | Linear ulcers on endoscopy, cotton-wool spots on fundoscopy<br>Biopsy reveals cells with intranuclear (owl eye) inclusion bodies |
| *Cryptococcus neoformans* | Meningitis | Encapsulated yeast on India ink stain or capsular antigen ⊕ |
| *Cryptosporidium* spp | Chronic, watery diarrhea | Acid-fast oocysts in stool |
| EBV | B-cell lymphoma (eg, non-Hodgkin lymphoma, CNS lymphoma) | CNS lymphoma—ring enhancing, may be solitary (vs *Toxoplasma*) |
| *Mycobacterium avium–intracellulare*, *Mycobacterium avium* complex | Nonspecific systemic symptoms (fever, night sweats, weight loss) or focal lymphadenitis | Most common if CD4+ cell count < 50/mm$^3$ |
| *Toxoplasma gondii* | Brain abscesses | Multiple ring-enhancing lesions on MRI |

**Prions**

Prion diseases are caused by the conversion of a normal (predominantly α-helical) protein termed prion protein ($PrP^c$) to a β-pleated form ($PrP^{sc}$), which is transmissible via CNS-related tissue (iatrogenic CJD) or food contaminated by BSE-infected animal products (variant CJD). $PrP^{sc}$ resists protease degradation and facilitates the conversion of still more $PrP^c$ to $PrP^{sc}$. Resistant to standard sterilizing procedures, including standard autoclaving. Accumulation of $PrP^{sc}$ results in spongiform encephalopathy and dementia, ataxia, startle myoclonus, and death.

**Creutzfeldt-Jakob disease**—rapidly progressive dementia, typically sporadic (some familial forms).

**Bovine spongiform encephalopathy**—also called "mad cow disease."

**Kuru**—acquired prion disease noted in tribal populations practicing human cannibalism.

## ▸ MICROBIOLOGY—SYSTEMS

**Normal flora: dominant**

Neonates delivered by C-section have no flora but are rapidly colonized after birth.

| LOCATION | MICROORGANISM |
|---|---|
| Skin | *S epidermidis* |
| Nose | *S epidermidis*; colonized by *S aureus* |
| Oropharynx | Viridans group streptococci |
| Dental plaque | *S mutans* |
| Colon | *B fragilis* > *E coli* |
| Vagina | *Lactobacillus*; colonized by *E coli* and group B strep |

**Bugs causing food-borne illness**

*S aureus* and *B cereus* food poisoning starts quickly and ends quickly.

| MICROORGANISM | SOURCE OF INFECTION |
|---|---|
| *B cereus* | Reheated rice. "Food poisoning from reheated rice? Be serious!" (*B cereus*) |
| *C botulinum* | Improperly canned foods (toxins), raw honey (spores) |
| *C perfringens* | Reheated meat |
| *E coli* O157:H7 | Undercooked meat |
| *L monocytogenes* | Deli meats, soft cheeses |
| *Salmonella* | Poultry, meat, and eggs |
| *S aureus* | Meats, mayonnaise, custard; preformed toxin |
| *V parahaemolyticus* and *V vulnificus*[a] | Raw/undercooked seafood |

[a] *V vulnificus* predominantly causes wound infections from contact with contaminated water or shellfish.

### Bugs causing diarrhea

| | |
|---|---|
| **Bloody diarrhea** | |
| *Campylobacter* | Comma- or S-shaped organisms; growth at 42°C |
| *E histolytica* | Protozoan; amebic dysentery; liver abscess |
| Enterohemorrhagic *E coli* | O157:H7; can cause HUS; makes Shiga toxin |
| Enteroinvasive *E coli* | Invades colonic mucosa |
| *Salmonella* (non-typhoidal) | Lactose ⊖; flagellar motility; has animal reservoir, especially poultry and eggs |
| *Shigella* | Lactose ⊖; very low $ID_{50}$; produces Shiga toxin; human reservoir only; bacillary dysentery |
| *Y enterocolitica* | Day care outbreaks; pseudoappendicitis |
| **Watery diarrhea** | |
| *C difficile* | Pseudomembranous colitis; associated with antibiotics and PPIs; occasionally bloody diarrhea |
| *C perfringens* | Also causes gas gangrene |
| Enterotoxigenic *E coli* | Travelers' diarrhea; produces heat-labile (LT) and heat-stable (ST) toxins |
| Protozoa | *Giardia*, *Cryptosporidium* |
| *V cholerae* | Comma-shaped organisms; rice-water diarrhea; often from infected seafood |
| Viruses | Norovirus (most common cause in developed countries), rotavirus (↓ incidence in developed countries due to vaccination), enteric adenovirus |

### Common causes of pneumonia

| NEONATES (< 4 WK) | CHILDREN (4 WK–18 YR) | ADULTS (18–40 YR) | ADULTS (40–65 YR) | ELDERLY |
|---|---|---|---|---|
| Group B streptococci<br>*E coli* | Viruses (RSV)<br>*Mycoplasma*<br>*C trachomatis* (infants–3 yr)<br>*C pneumoniae* (school-aged children)<br>*S pneumoniae*<br>Runts May Cough Chunky Sputum | *Mycoplasma*<br>*C pneumoniae*<br>*S pneumoniae*<br>Viruses (eg, influenza) | *S pneumoniae*<br>*H influenzae*<br>Anaerobes<br>Viruses<br>*Mycoplasma* | *S pneumoniae*<br>Influenza virus<br>Anaerobes<br>*H influenzae*<br>Gram ⊖ rods |

| | |
|---|---|
| **Special groups** | |
| Alcohol overuse | *Klebsiella*, anaerobes usually due to aspiration (eg, *Peptostreptococcus*, *Fusobacterium*, *Prevotella*, *Bacteroides*) |
| IV drug use | *S pneumoniae*, *S aureus* |
| Aspiration | Anaerobes |
| Atypical | *Mycoplasma*, *Chlamydophila*, *Legionella*, viruses (RSV, CMV, influenza, adenovirus) |
| Cystic fibrosis | *Pseudomonas*, *S aureus*, *S pneumoniae*, *Burkholderia cepacia* |
| Immunocompromised | *S aureus*, enteric gram ⊖ rods, fungi, viruses, *P jirovecii* (with HIV) |
| Nosocomial | *S aureus*, *Pseudomonas*, other enteric gram ⊖ rods |
| Postviral | *S pneumoniae*, *S aureus*, *H influenzae* |
| COPD | *S pneumoniae*, *H influenzae*, *M catarrhalis*, *Pseudomonas* |

## Common causes of meningitis

| NEWBORN (0–6 MO) | CHILDREN (6 MO–6 YR) | 6–60 YR | 60 YR + |
|---|---|---|---|
| Group B *Streptococcus*<br>*E coli*<br>*Listeria* | *S pneumoniae*<br>*N meningitidis*<br>*H influenzae* type b<br>Group B *Streptococcus*<br>Enteroviruses | *S pneumoniae*<br>*N meningitidis*<br>Enteroviruses<br>HSV | *S pneumoniae*<br>*N meningitidis*<br>*H influenzae* type b<br>Group B *Streptococcus*<br>*Listeria* |

Give ceftriaxone and vancomycin empirically (add ampicillin if *Listeria* is suspected).

Viral causes of meningitis: enteroviruses (especially coxsackievirus), HSV-2 (HSV-1 = encephalitis), HIV, West Nile virus (also causes encephalitis), VZV.

In HIV: *Cryptococcus* spp.

Note: Incidence of Group B streptococcal meningitis in neonates has ↓ greatly due to screening and antibiotic prophylaxis in pregnancy. Incidence of *H influenzae* meningitis has ↓ greatly due to conjugate *H influenzae* vaccinations. Today, cases are usually seen in unimmunized children.

## Cerebrospinal fluid findings in meningitis

| | OPENING PRESSURE | CELL TYPE | PROTEIN | GLUCOSE |
|---|---|---|---|---|
| **Bacterial** | ↑ | ↑ PMNs | ↑ | ↓ |
| **Fungal/TB** | ↑ | ↑ lymphocytes | ↑ | ↓ |
| **Viral** | Normal/↑ | ↑ lymphocytes | Normal/↑ | Normal |

## Infections causing brain abscess

Most commonly viridans streptococci and *Staphylococcus aureus*. If dental infection or extraction precedes abscess, oral anaerobes commonly involved.

Multiple abscesses are usually from bacteremia; single lesions from contiguous sites: otitis media and mastoiditis → temporal lobe and cerebellum; sinusitis or dental infection → frontal lobe.

*Toxoplasma* reactivation in AIDS.

## Osteomyelitis


| RISK FACTOR | ASSOCIATED INFECTION |
|---|---|
| Assume if no other information is available | *S aureus* (most common overall) |
| Sexually active | *Neisseria gonorrhoeae* (rare), septic arthritis more common |
| Sickle cell disease | *Salmonella* and *S aureus* |
| Prosthetic joint replacement | *S aureus* and *S epidermidis* |
| Vertebral involvement | *S aureus*, *M tuberculosis* (Pott disease) |
| Cat and dog bites | *Pasteurella multocida* |
| IV drug use | *S aureus*; also *Pseudomonas*, *Candida* |

Elevated ESR and CRP sensitive but not specific.

Radiographs are insensitive early but can be useful in chronic osteomyelitis (A, left). MRI is best for detecting acute infection and detailing anatomic involvement (A, right). Biopsy or aspiration with culture necessary to identify organism.

### Urinary tract infections

Cystitis presents with dysuria, frequency, urgency, suprapubic pain, and WBCs (but not WBC casts) in urine. Primarily caused by ascension of microbes from urethra to bladder. Ascension to kidney results in pyelonephritis, which presents with fever, chills, flank pain, costovertebral angle tenderness, hematuria, and WBC casts.

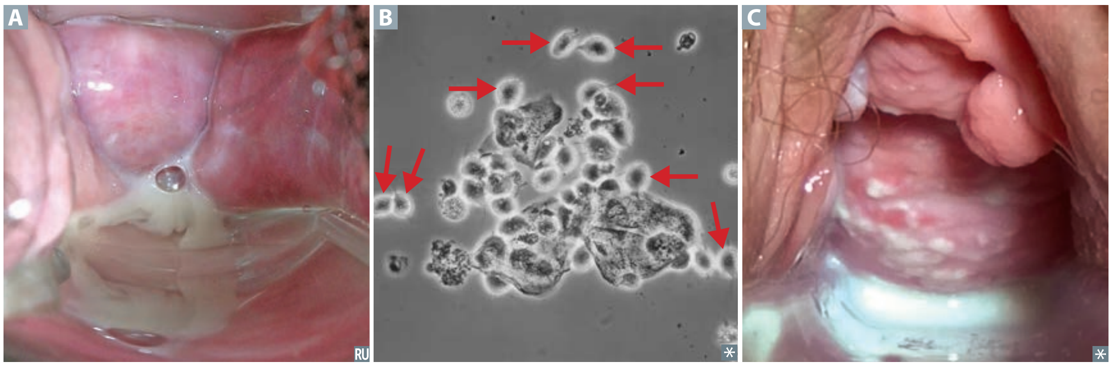
Ten times more common in females (shorter urethras colonized by fecal flora).

Risk factors: obstruction (eg, kidney stones, enlarged prostate), kidney surgery, catheterization, congenital GU malformation (eg, vesicoureteral reflux), diabetes, pregnancy.

| SPECIES | FEATURES | COMMENTS |
|---|---|---|
| *Escherichia coli* | Leading cause of UTI. Colonies show strong pink lactose-fermentation on MacConkey agar. | Diagnostic markers:<br>⊕ Leukocyte esterase = evidence of WBC activity.<br>⊕ Nitrite test = reduction of urinary nitrates by gram ⊖ bacterial species (eg, *E coli*). |
| *Staphylococcus saprophyticus* | 2nd leading cause of UTI, particularly in young, sexually active females. | |
| *Klebsiella pneumoniae* | 3rd leading cause of UTI. Large mucoid capsule and viscous colonies. | |
| *Serratia marcescens* | Some strains produce a red pigment; often nosocomial and drug resistant. | |
| *Enterococcus* | Often nosocomial and drug resistant. | |
| *Proteus mirabilis* | Motility causes "swarming" on agar; associated with struvite stones. Produces urease. | |
| *Pseudomonas aeruginosa* | Blue-green pigment and fruity odor; usually nosocomial and drug resistant. | |

### Common vaginal infections

| | Bacterial vaginosis | *Trichomonas* vaginitis | *Candida* vulvovaginitis |
|---|---|---|---|
| SIGNS AND SYMPTOMS | No inflammation<br>Thin, white discharge A with fishy odor | Inflammation ("strawberry cervix")<br>Frothy, yellow-green, foul-smelling discharge | Inflammation<br>Thick, white, "cottage cheese" discharge C |
| LAB FINDINGS | Clue cells<br>pH > 4.5<br>⊕ KOH whiff test | Motile pear-shaped trichomonads B<br>pH > 4.5 | Pseudohyphae<br>pH normal (4.0–4.5) |
| TREATMENT | Metronidazole or clindamycin | Metronidazole<br>Treat sexual partner(s) | Azoles |



### TORCH infections

Microbes that may pass from mother to fetus. Transmission is transplacental in most cases, or via vaginal delivery (especially HSV-2). Nonspecific signs common to many **ToRCHHeS** infections include hepatosplenomegaly, jaundice, thrombocytopenia, and growth restriction.

Other important infectious agents include *Streptococcus agalactiae* (group B streptococci), *E coli*, and *Listeria monocytogenes*—all causes of meningitis in neonates. Parvovirus B19 causes hydrops fetalis.

| AGENT | MATERNAL ACQUISITION | MATERNAL MANIFESTATIONS | NEONATAL MANIFESTATIONS |
|---|---|---|---|
| ***To**xoplasma gondii* | Cat feces or ingestion of undercooked meat | Usually asymptomatic; lymphadenopathy (rarely) | Classic triad: chorioretinitis, hydrocephalus, and intracranial calcifications, +/– "blueberry muffin" rash A |
| **R**ubella | Respiratory droplets | Rash, lymphadenopathy, polyarthritis, polyarthralgia | Classic triad: abnormalities of **eye** (cataracts B) and **ear** (deafness) and congenital **heart** disease (PDA); +/– "blueberry muffin" rash. "**I** (eye) ♥ **ruby** (**rub**ella) **ear**rings" |
| **C**ytomegalovirus | Sexual contact, organ transplants | Usually asymptomatic; mononucleosis-like illness | Hearing loss, seizures, petechial rash, "blueberry muffin" rash, chorioretinitis, periventricular calcifications C |
| **H**IV | Sexual contact, needlestick | Variable presentation depending on CD4+ cell count | Recurrent infections, chronic diarrhea |
| **He**rpes simplex virus-2 | Skin or mucous membrane contact | Usually asymptomatic; herpetic (vesicular) lesions | Meningoencephalitis, herpetic (vesicular) lesions |
| **S**yphilis | Sexual contact | Chancre (1°) and disseminated rash (2°) are the two stages likely to result in fetal infection | Often results in stillbirth, hydrops fetalis; if child survives, presents with facial abnormalities (eg, notched teeth, saddle nose, short maxilla), saber shins, CN VIII deafness |



### Red rashes of childhood

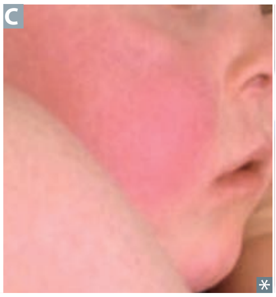
| AGENT | ASSOCIATED SYNDROME/DISEASE | CLINICAL PRESENTATION |
|---|---|---|
| Coxsackievirus type A | Hand-foot-mouth disease | Oval-shaped vesicles on palms and soles A; vesicles and ulcers in oral mucosa (herpangina) |
| Human herpesvirus 6 | Roseola (exanthem subitum) | Asymptomatic rose-colored macules appear on body after several days of high fever; can present with febrile seizures; usually affects infants |
| Measles virus | Measles (rubeola) | Confluent rash beginning at head and moving down; preceded by cough, coryza, conjunctivitis, and blue-white (Koplik) spots on buccal mucosa |
| Parvovirus B19 | Erythema infectiosum (fifth disease) | "Slapped cheek" rash on face B (can cause hydrops fetalis in pregnant patients) |
| Rubella virus | Rubella | Pink macules and papules begin at head and move down, remain discrete → fine desquamating truncal rash; postauricular lymphadenopathy |
| *Streptococcus pyogenes* | Scarlet fever | **S**ore throat, **C**ircumoral pallor C, group **A** strep, **R**ash (sandpaper-like, from neck to trunk and extremities), **L**ymphadenopathy, **E**rythrogenic toxin, strawberry **T**ongue (**SCARLET**) |
| Varicella-Zoster virus | Chickenpox | Vesicular rash begins on trunk; spreads to face D and extremities with lesions of different stages |

A



B



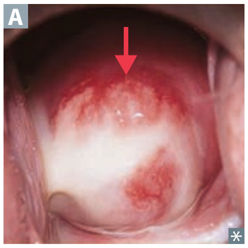
C


D


## Sexually transmitted infections

| DISEASE | CLINICAL FEATURES | PATHOGEN |
|---|---|---|
| AIDS | Opportunistic infections, Kaposi sarcoma, lymphoma | HIV |
| Chancroid  | Painful genital ulcer with exudate, inguinal adenopathy A | *Haemophilus* ***ducreyi*** (it's so painful, you "**do cry**") |
| Chlamydia | Urethritis, cervicitis, epididymitis, conjunctivitis, reactive arthritis, PID | *Chlamydia trachomatis* (D–K) |
| Condylomata acuminata | Genital warts, koilocytes | HPV-6 and -11 |
| Genital herpes | Painful penile, vulvar, or cervical vesicles and ulcers; can cause systemic symptoms such as fever, headache, myalgia | HSV-2, less commonly HSV-1 |
| Gonorrhea | Urethritis, cervicitis, PID, prostatitis, epididymitis, arthritis, creamy purulent discharge | *Neisseria gonorrhoeae* |
| Granuloma inguinale (Donovanosis)  | Painless, beefy red ulcer that bleeds readily on contact B<br>Uncommon in US | *Klebsiella (Calymmatobacterium) granulomatis;* cytoplasmic Donovan bodies (bipolar staining) seen on microscopy |
| Hepatitis B | Jaundice | HBV |
| Lymphogranuloma venereum | Infection of lymphatics; painless genital ulcers, painful lymphadenopathy (ie, buboes) | *C trachomatis* (L1–L3) |
| Primary syphilis | Painless chancre | *Treponema pallidum* |
| Secondary syphilis | Fever, lymphadenopathy, skin rashes, condylomata lata | |
| Tertiary syphilis | Gummas, tabes dorsalis, general paresis, aortitis, Argyll Robertson pupil | |
| Trichomoniasis | Vaginitis, strawberry cervix, motile in wet prep | *Trichomonas vaginalis* |

**Pelvic inflammatory disease**

A


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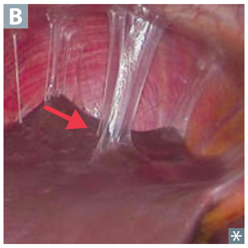


Top bugs—*Chlamydia trachomatis* (subacute, often undiagnosed), *Neisseria gonorrhoeae* (acute).
*C trachomatis*—most common bacterial STI in the United States.
Signs include cervical motion tenderness, adnexal tenderness, purulent cervical discharge A.
PID may include salpingitis, endometritis, hydrosalpinx, and tubo-ovarian abscess.

Salpingitis is a risk factor for ectopic pregnancy, infertility, chronic pelvic pain, and adhesions.
Can lead to perihepatitis (**Fitz-Hugh–Curtis syndrome**)—infection and inflammation of liver capsule and “violin string” adhesions of peritoneum to liver B.

**Nosocomial infections** *E coli* (UTI) and *S aureus* (wound infection) are the two most common causes.

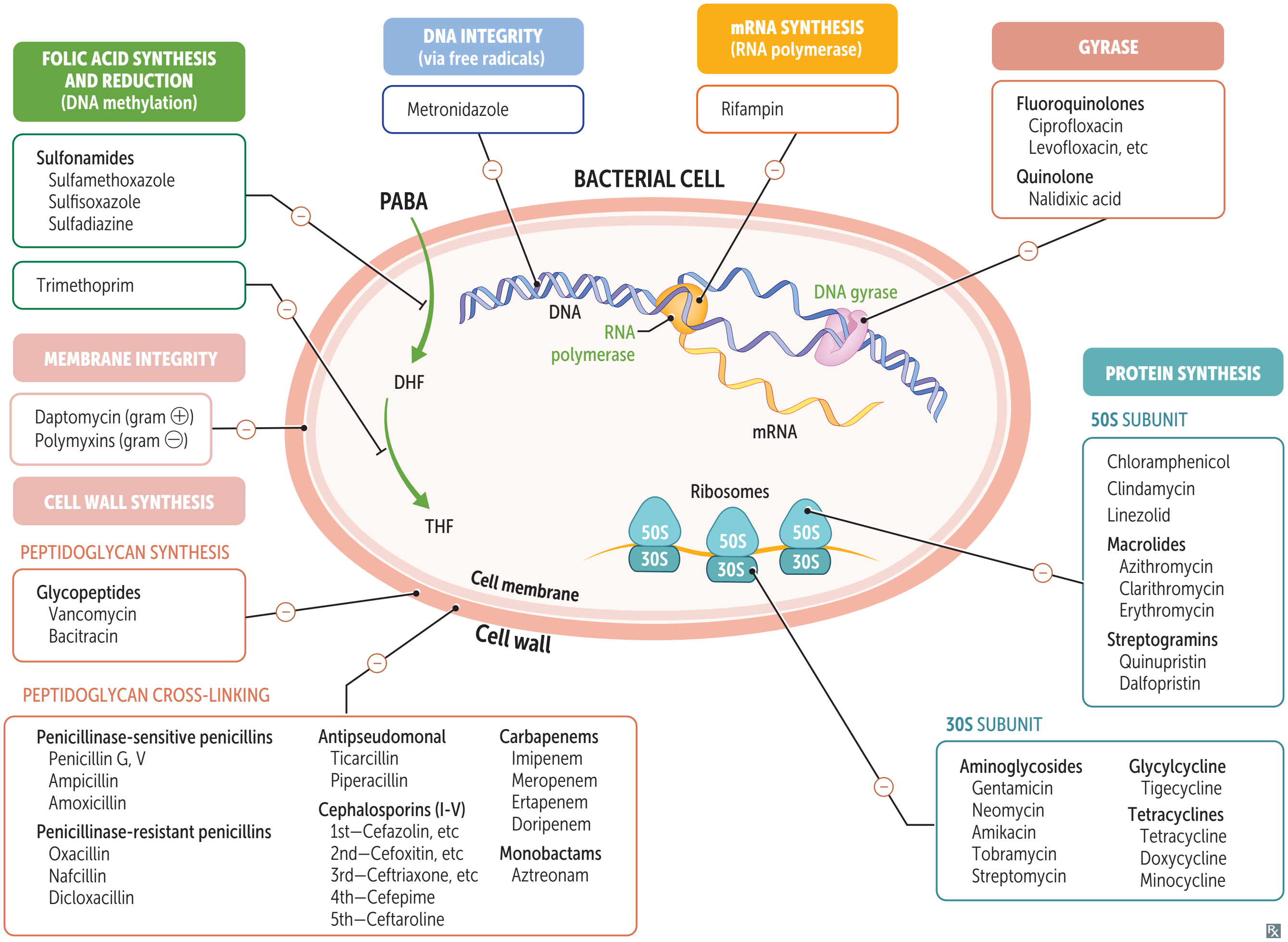
| RISK FACTOR | PATHOGEN | UNIQUE SIGNS/SYMPTOMS |
|---|---|---|
| Antibiotic use | *Clostridium difficile* | Watery diarrhea, leukocytosis |
| Aspiration (2° to altered mental status, old age) | Polymicrobial, gram ⊖ bacteria, often anaerobes | Right lower lobe infiltrate or right upper/middle lobe (patient recumbent); purulent malodorous sputum |
| Decubitus ulcers, surgical wounds, drains | *S aureus* (including MRSA), gram ⊖ anaerobes (*Bacteroides*, *Prevotella*, *Fusobacterium*) | Erythema, tenderness, induration, drainage from surgical wound sites |
| Intravascular catheters | *S aureus* (including MRSA), *S epidermidis* (long term) | Erythema, induration, tenderness, drainage from access sites |
| Mechanical ventilation, endotracheal intubation | Late onset: *P aeruginosa*, *Klebsiella*, *Acinetobacter*, *S aureus* | New infiltrate on CXR, ↑ sputum production; sweet odor (*Pseudomonas*) |
| Renal dialysis unit, needlestick | HBV, HCV | |
| Urinary catheterization | ***P****roteus* spp, ***E*** *coli*, ***K****lebsiella* (**PEcK**) | Dysuria, leukocytosis, flank pain or costovertebral angle tenderness |
| Water aerosols | *Legionella* | Signs of pneumonia, GI symptoms (diarrhea, nausea, vomiting), neurologic abnormalities |

### Bugs affecting unvaccinated children

| CLINICAL PRESENTATION | FINDINGS/LABS | PATHOGEN |
| --- | --- | --- |
| **Dermatologic** | | |
| **Rash** | Beginning at head and moving down with postauricular lymphadenopathy | Rubella virus |
| | Beginning at head and moving down; preceded by cough, coryza, conjunctivitis, and Koplik spots | Measles virus |
| **Neurologic** | | |
| **Meningitis** | Microbe colonizes nasopharynx | *H influenzae* type b |
| | Can also lead to myalgia and paralysis | Poliovirus |
| **Tetanus** | Muscle spasms and spastic paralysis (eg, lockjaw, opisthotonus) | *Clostridium tetani* |
| **Respiratory** | | |
| **Epiglottitis** | Fever with dysphagia, drooling, and difficulty breathing due to edema | *H influenzae* type b (also capable of causing epiglottitis in fully immunized children) |
| **Pertussis** | Low-grade fevers, coryza → whooping cough, posttussive vomiting → gradual recovery | *Bordetella pertussis* |
| **Pharyngitis** | Grayish pseudomembranes (may obstruct airways) | *Corynebacterium diphtheriae* |

## ▸ MICROBIOLOGY—ANTIMICROBIALS

### Antimicrobial therapy




| | |
|---|---|
| **Penicillin G, V** | Penicillin G (IV and IM form), penicillin V (oral). Prototype β-lactam antibiotics. |
| MECHANISM | D-Ala-D-Ala structural analog. Bind penicillin-binding proteins (transpeptidases).<br>Block transpeptidase cross-linking of peptidoglycan in cell wall.<br>Activate autolytic enzymes. |
| CLINICAL USE | Mostly used for gram ⊕ organisms (*S pneumoniae*, *S pyogenes*, *Actinomyces*). Also used for gram ⊖ cocci (mainly *N meningitidis*) and spirochetes (mainly *T pallidum*). Bactericidal for gram ⊕ cocci, gram ⊕ rods, gram ⊖ cocci, and spirochetes. β-lactamase sensitive. |
| ADVERSE EFFECTS | Hypersensitivity reactions, direct Coombs ⊕ hemolytic anemia, drug-induced interstitial nephritis. |
| RESISTANCE | β-lactamase cleaves the β-lactam ring. Mutations in PBPs. |

| **Penicillinase-sensitive penicillins** | Amoxicillin, ampicillin; aminopenicillins. | |
|---|---|---|
| MECHANISM | Same as penicillin. Wider spectrum; penicillinase sensitive. Also combine with clavulanic acid to protect against destruction by β-lactamase. | **Am**ino**p**enicillins are **amp**ed-up penicillin. Am**o**xicillin has greater **o**ral bioavailability than ampicillin. |
| CLINICAL USE | Extended-spectrum penicillin—***H*** *influenzae*, ***H*** *pylori*, ***E*** *coli*, **E**nterococci, ***L****isteria monocytogenes*, ***P****roteus mirabilis*, ***S****almonella*, ***S****higella*. | Coverage: ampicillin/amoxicillin **HHEELPSS** kill enterococci. |
| ADVERSE EFFECTS | Hypersensitivity reactions, rash, pseudomembranous colitis. | |
| MECHANISM OF RESISTANCE | Penicillinase (a type of β-lactamase) cleaves β-lactam ring. | |

| **Penicillinase-resistant penicillins** | Dicloxacillin, nafcillin, oxacillin. | |
|---|---|---|
| MECHANISM | Same as penicillin. Narrow spectrum; penicillinase resistant because bulky R group blocks access of β-lactamase to β-lactam ring. | |
| CLINICAL USE | *S aureus* (except MRSA). | "Use **naf** (nafcillin) for **staph**." |
| ADVERSE EFFECTS | Hypersensitivity reactions, interstitial nephritis. | |
| MECHANISM OF RESISTANCE | MRSA has altered penicillin-binding protein target site. | |

| **Antipseudomonal penicillins** | Piperacillin, ticarcillin. |
|---|---|
| MECHANISM | Same as penicillin. Extended spectrum. Penicillinase sensitive; use with β-lactamase inhibitors. |
| CLINICAL USE | *Pseudomonas* spp. and gram ⊖ rods. |
| ADVERSE EFFECTS | Hypersensitivity reactions. |

## Cephalosporins

| | | |
|---|---|---|
| MECHANISM | β-lactam drugs that inhibit cell wall synthesis but are less susceptible to penicillinases. Bactericidal. | Organisms typically not covered by 1st–4th generation cephalosporins are **LAME**: ***L**isteria*, **A**typicals (*Chlamydia*, *Mycoplasma*), **M**RSA, and **E**nterococci. |
| CLINICAL USE | 1st generation (cefazolin, cephalexin)—gram ⊕ cocci, ***P**roteus mirabilis*, ***E** coli*, ***K**lebsiella pneumoniae*. Cefazolin used prior to surgery to prevent *S aureus* wound infections. | 1st generation—⊕ **PEcK**. |
| | **2nd** generation (ce**fa**clor, ce**fox**itin, ce**fur**oxime, cefo**te**tan)—gram ⊕ cocci, ***H** influenzae*, ***E**nterobacter aerogenes*, ***N**eisseria* spp., ***S**erratia marcescens*, ***P**roteus mirabilis*, ***E** coli*, ***K**lebsiella pneumoniae*. | **2nd** graders wear **fa**ke **fox fur** to **te**a parties. 2nd generation—⊕ **HENS PEcK**. |
| | 3rd generation (ceftriaxone, cefotaxime, cefpodoxime, ceftazidime, cefixime)—serious gram ⊖ infections resistant to other β-lactams. | Can cross blood-brain barrier. Ceftriaxone—meningitis, gonorrhea, disseminated Lyme disease. Ceftazidime—*Pseudomonas*. |
| | 4th generation (cefepime)—gram ⊖ organisms, with ↑ activity against *Pseudomonas* and gram ⊕ organisms. | |
| | 5th generation (ceftaroline)—broad gram ⊕ and gram ⊖ organism coverage; unlike 1st–4th generation cephalosporins, ceftaroline covers MRSA, and *Enterococcus faecalis*—does not cover *Pseudomonas*. | |
| ADVERSE EFFECTS | Hypersensitivity reactions, autoimmune hemolytic anemia, disulfiram-like reaction, vitamin K deficiency. Low rate of cross-reactivity even in penicillin-allergic patients. ↑ nephrotoxicity of aminoglycosides. | |
| MECHANISM OF RESISTANCE | Inactivated by cephalosporinases (a type of β-lactamase). Structural change in penicillin-binding proteins (transpeptidases). | |

| | | |
|---|---|---|
| **β-lactamase inhibitors** | Include **C**lavulanic acid, **A**vibactam, **S**ulbactam, **T**azobactam. Often added to penicillin antibiotics to protect the antibiotic from destruction by β-lactamase. | **CAST** (eg, amoxicillin-clavulanate, ceftazidime-avibactam, ampicillin-sulbactam, piperacillin-tazobactam). |

## Carbapenems

| | | |
|---|---|---|
| **Carbapenems** | **D**oripenem, **i**mipenem, **m**eropenem, **e**rtapenem. | "**Pens**" (carba**pen**ems) cost a **dime**." |
| MECHANISM | Imipenem is a broad-spectrum, β-lactamase–resistant carbapenem. Always administered with cilastatin (inhibitor of renal dehydropeptidase I) to ↓ inactivation of drug in renal tubules. | With imipenem, "the kill is **lastin**' with ci**lastatin**." Newer carbapenems include ertapenem (limited *Pseudomonas* coverage) and doripenem. |
| CLINICAL USE | Gram ⊕ cocci, gram ⊖ rods, and anaerobes. Wide spectrum and significant side effects limit use to life-threatening infections or after other drugs have failed. Meropenem has a ↓ risk of seizures and is stable to dehydropeptidase I. | |
| ADVERSE EFFECTS | GI distress, rash, and CNS toxicity (seizures) at high plasma levels. | |
| MECHANISM OF RESISTANCE | Inactivated by carbapenemases produced by, eg, *K pneumoniae*, *E coli*, *E aerogenes*. | |

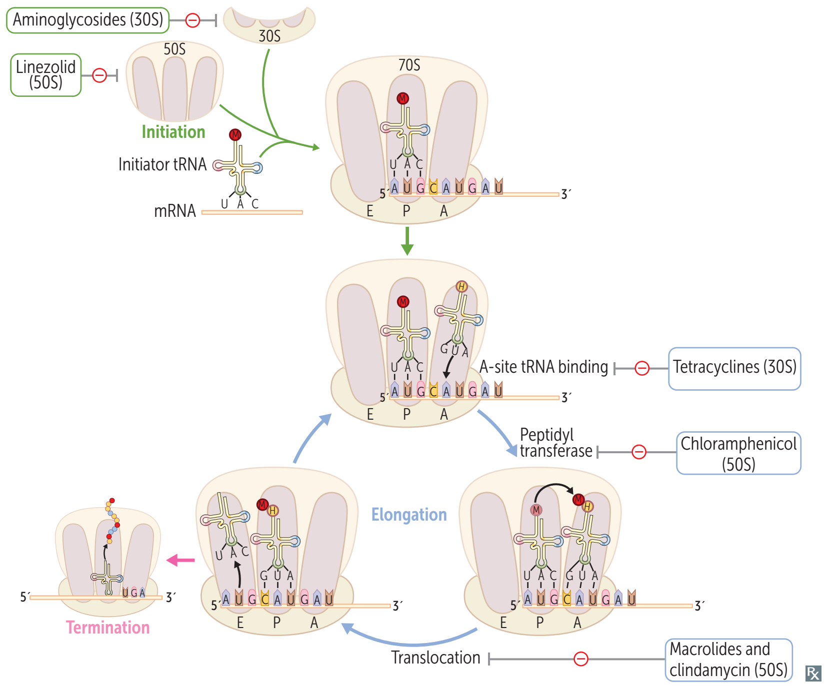
## Aztreonam

| | |
|---|---|
| MECHANISM | Less susceptible to β-lactamases. Prevents peptidoglycan cross-linking by binding to penicillin-binding protein 3. Synergistic with aminoglycosides. No cross-allergenicity with penicillins. |
| CLINICAL USE | Gram ⊖ rods only—no activity against gram ⊕ rods or anaerobes. For penicillin-allergic patients and those with renal insufficiency who cannot tolerate aminoglycosides. |
| ADVERSE EFFECTS | Usually nontoxic; occasional GI upset. |

## Vancomycin

| | |
|---|---|
| MECHANISM | Inhibits cell wall peptidoglycan formation by binding D-Ala-D-Ala portion of cell wall precursors. Bactericidal against most bacteria (bacteriostatic against *C difficile*). Not susceptible to β-lactamases. |
| CLINICAL USE | Gram ⊕ bugs only—for serious, multidrug-resistant organisms, including MRSA, *S epidermidis*, sensitive *Enterococcus* species, and *Clostridium difficile* (oral route). |
| ADVERSE EFFECTS  | Well tolerated in general but **not** trouble **f**ree: **n**ephrotoxicity, **o**totoxicity, **t**hrombophlebitis, diffuse **f**lushing (red man syndrome A idiopathic reaction largely preventable by pretreatment with antihistamines), DRESS syndrome. |
| MECHANISM OF RESISTANCE | Occurs in bacteria (eg, *Enterococcus*) via amino acid modification of D-Ala-D-Ala to **D-Ala**-D-**Lac**. "If you **Lack** a **D-Ala** (dollar), you can't ride the **van** (**van**comycin)." |

## Protein synthesis inhibitors




Specifically target smaller bacterial ribosome (70S, made of 30S and 50S subunits), leaving human ribosome (80S) unaffected.

**All are bacteriostatic, except aminoglycosides (bactericidal) and linezolid (variable).**

### 30S inhibitors

**A**minoglycosides
**T**etracyclines

### 50S inhibitors

**C**hloramphenicol, **cl**indamycin
**e**rythromycin (macrolides)
**l**inezolid

"Buy **at 30**, **ccel** (sell) at **50**."

| **Aminoglycosides** | **G**entamicin, **N**eomycin, **A**mikacin, **T**obramycin, **S**treptomycin. | "**Mean**" (**amin**oglycoside) **GNATS** **cannot** kill anaerobes. |
|---|---|---|
| MECHANISM | Bactericidal; irreversible inhibition of initiation complex through binding of the 30S subunit. Can cause misreading of mRNA. Also block translocation. Require $O_2$ for uptake; therefore ineffective against anaerobes. | |
| CLINICAL USE | Severe gram ⊖ rod infections. Synergistic with β-lactam antibiotics.<br>Neomycin for bowel surgery. | |
| ADVERSE EFFECTS | **N**ephrotoxicity, **n**euromuscular blockade (absolute contraindication with myasthenia gravis), **o**totoxicity (especially with loop diuretics), **t**eratogenicity. | |
| MECHANISM OF RESISTANCE | Bacterial transferase enzymes inactivate the drug by acetylation, phosphorylation, or adenylation. | |

| **Tetracyclines** | Tetracycline, doxycycline, minocycline. |
|---|---|
| MECHANISM | Bacteriostatic; bind to 30S and prevent attachment of aminoacyl-tRNA. Limited CNS penetration. Doxycycline is fecally eliminated and can be used in patients with renal failure. Do not take tetracyclines with milk ($Ca^{2+}$), antacids (eg, $Ca^{2+}$ or $Mg^{2+}$), or iron-containing preparations because divalent cations inhibit drugs' absorption in the gut. |
| CLINICAL USE | *Borrelia burgdorferi*, *M pneumoniae*. Drugs' ability to accumulate intracellularly makes them very effective against *Rickettsia* and *Chlamydia*. Also used to treat acne. Doxycycline effective against community-acquired MRSA. |
| ADVERSE EFFECTS | GI distress, discoloration of teeth and inhibition of bone growth in children, photosensitivity. "**Teratoc**ylines" are **terato**genic; generally avoided in pregnancy and in children (except doxycycline). |
| MECHANISM OF RESISTANCE | ↓ uptake or ↑ efflux out of bacterial cells by plasmid-encoded transport pumps. |

| **Tigecycline** | |
|---|---|
| MECHANISM | Tetracycline derivative. Binds to 30S, inhibiting protein synthesis. Generally bacteriostatic. |
| CLINICAL USE | Broad-spectrum anaerobic, gram ⊖, and gram ⊕ coverage. Multidrug-resistant organisms (MRSA, VRE) or infections requiring deep tissue penetration. |
| ADVERSE EFFECTS | Nausea, vomiting. |

| **Chloramphenicol** | |
|---|---|
| MECHANISM | Blocks peptidyltransferase at 50S ribosomal subunit. Bacteriostatic. |
| CLINICAL USE | Meningitis (*Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*) and rickettsial diseases (eg, Rocky Mountain spotted fever [*Rickettsia rickettsii*]).<br>Limited use due to toxicity but often still used in developing countries because of low cost. |
| ADVERSE EFFECTS | Anemia (dose dependent), aplastic anemia (dose independent), gray baby syndrome (in premature infants because they lack liver UDP-glucuronosyltransferase). |
| MECHANISM OF RESISTANCE | Plasmid-encoded acetyltransferase inactivates the drug. |

| **Clindamycin** | |
|---|---|
| MECHANISM | Blocks peptide transfer (translocation) at 50S ribosomal subunit. Bacteriostatic. |
| CLINICAL USE | Anaerobic infections (eg, *Bacteroides* spp., *Clostridium perfringens*) in aspiration pneumonia, lung abscesses, and oral infections. Also effective against invasive group A streptococcal infection.<br>Treats anaerobic infections above the diaphragm vs metronidazole (anaerobic infections below diaphragm). |
| ADVERSE EFFECTS | Pseudomembranous colitis (*C difficile* overgrowth), fever, diarrhea. |

## Linezolid

| | |
|---|---|
| MECHANISM | Inhibits protein synthesis by binding to 50S subunit and preventing formation of the initiation complex. |
| CLINICAL USE | Gram ⊕ species including MRSA and VRE. |
| ADVERSE EFFECTS | Bone marrow suppression (especially thrombocytopenia), peripheral neuropathy, serotonin syndrome (due to partial MAO inhibition). |
| MECHANISM OF RESISTANCE | Point mutation of ribosomal RNA. |

## Macrolides

Azithromycin, clarithromycin, erythromycin.

| | |
|---|---|
| MECHANISM | Inhibit protein synthesis by blocking **trans**location ("macro**slides**"); bind to the 23S rRNA of the 50S ribosomal subunit. Bacteriostatic. |
| CLINICAL USE | Atypical pneumonias (*Mycoplasma*, *Chlamydia*, *Legionella*), STIs (*Chlamydia*), gram ⊕ cocci (streptococcal infections in patients allergic to penicillin), and *B pertussis*. |
| ADVERSE EFFECTS | **MACRO**: Gastrointestinal **M**otility issues, **A**rrhythmia caused by prolonged QT interval, acute **C**holestatic hepatitis, **R**ash, e**O**sinophilia. Increases serum concentration of theophylline, oral anticoagulants. Clarithromycin and erythromycin inhibit cytochrome P-450. |
| MECHANISM OF RESISTANCE | Methylation of 23S rRNA-binding site prevents binding of drug. |

## Polymyxins

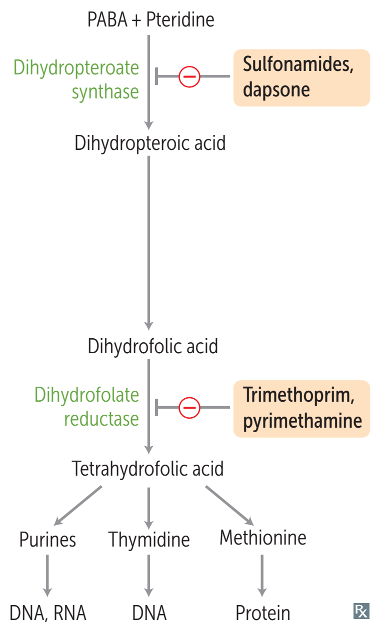
Colistin (polymyxin E), polymyxin B.

| | |
|---|---|
| MECHANISM | Cation polypeptides that bind to phospholipids on cell membrane of gram ⊖ bacteria. Disrupt cell membrane integrity → leakage of cellular components → cell death. |
| CLINICAL USE | Salvage therapy for multidrug-resistant gram ⊖ bacteria (eg, *P aeruginosa*, *E coli*, *K pneumoniae*). Polymyxin B is a component of a triple antibiotic ointment used for superficial skin infections. |
| ADVERSE EFFECTS | Nephrotoxicity, neurotoxicity (eg, slurred speech, weakness, paresthesias), respiratory failure. |

## Sulfonamides

Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine.

| | |
|---|---|
| MECHANISM | Inhibit dihydropteroate synthase, thus inhibiting folate synthesis. Bacteriostatic (bactericidal when combined with trimethoprim). |
| CLINICAL USE | Gram ⊕, gram ⊖, *Nocardia*. TMP-SMX for simple UTI. |
| ADVERSE EFFECTS | Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity (tubulointerstitial nephritis), photosensitivity, Stevens-Johnson syndrome, kernicterus in infants, displace other drugs from albumin (eg, warfarin). |
| MECHANISM OF RESISTANCE | Altered enzyme (bacterial dihydropteroate synthase), ↓ uptake, or ↑ PABA synthesis. |




## Dapsone

| | |
|---|---|
| MECHANISM | Similar to sulfonamides, but structurally distinct agent. |
| CLINICAL USE | Leprosy (lepromatous and tuberculoid), *Pneumocystis jirovecii* prophylaxis, or treatment when used in combination with TMP. |
| ADVERSE EFFECTS | Hemolysis if G6PD deficient, methemoglobinemia, agranulocytosis. |

## Trimethoprim

| | |
|---|---|
| MECHANISM | Inhibits bacterial dihydrofolate reductase. Bacteriostatic. |
| CLINICAL USE | Used in combination with sulfonamides (trimethoprim-sulfamethoxazole [TMP-SMX]), causing sequential block of folate synthesis. Combination used for UTIs, *Shigella*, *Salmonella*, *Pneumocystis jirovecii* pneumonia treatment and prophylaxis, toxoplasmosis prophylaxis. |
| ADVERSE EFFECTS | Hyperkalemia (high doses), megaloblastic anemia, leukopenia, granulocytopenia, which may be avoided with coadministration of leucovorin (folinic acid). **TMP T**reats **M**arrow **P**oorly. |

## Fluoroquinolones

Ciprofloxacin, enoxacin, norfloxacin, ofloxacin; respiratory fluoroquinolones: gemifloxacin, levofloxacin, moxifloxacin.

| | | |
|---|---|---|
| MECHANISM | Inhibit prokaryotic enzymes topoisomerase II (DNA gyrase) and topoisomerase IV. Bactericidal. Must not be taken with antacids. | |
| CLINICAL USE | Gram ⊖ rods of urinary and GI tracts (including *Pseudomonas*), some gram ⊕ organisms, otitis externa. | |
| ADVERSE EFFECTS | GI upset, superinfections, skin rashes, headache, dizziness. Less commonly, can cause leg cramps and myalgias.<br>Contraindicated during pregnancy or breastfeeding and in children < 18 years old due to possible damage to cartilage. Some may prolong QT interval. | May cause tendonitis or tendon rupture in people > 60 years old and in patients taking prednisone. Ciprofloxacin inhibits cytochrome P-450.<br>Fluoroquino**lones** hurt attachments to your **bones**. |
| MECHANISM OF RESISTANCE | Chromosome-encoded mutation in DNA gyrase, plasmid-mediated resistance, efflux pumps. | |

## Daptomycin

| | | |
|---|---|---|
| MECHANISM | Lipopeptide that disrupts cell membranes of gram ⊕ cocci by creating transmembrane channels. | |
| CLINICAL USE | *S aureus* skin infections (especially MRSA), bacteremia, endocarditis, VRE. | Not used for pneumonia (avidly binds to and is inactivated by surfactant). "Dapto-**myo**-**skin**" is used for **skin** infections but can cause **myo**pathy. |
| ADVERSE EFFECTS | Myopathy, rhabdomyolysis. | |

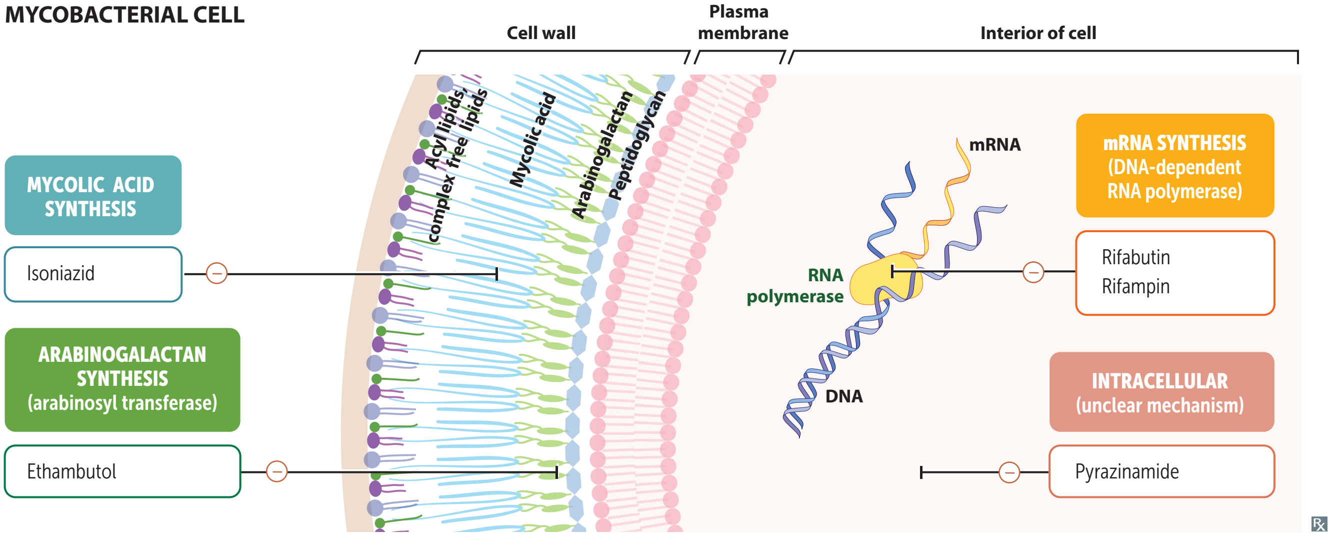
## Metronidazole

| | | |
|---|---|---|
| MECHANISM | Forms toxic free radical metabolites in the bacterial cell that damage DNA. Bactericidal, antiprotozoal. | |
| CLINICAL USE | Treats ***G**iardia*, ***E**ntamoeba*, ***T**richomonas*, ***G**ardnerella vaginalis*, **A**naerobes (*Bacteroides*, *C difficile*). Can be used in place of amoxicillin in *H **p**ylori* "triple therapy" in case of penicillin allergy. | **GET GAP** on the **Metro** with **metro**nidazole!<br>Treats anaerobic infection **below** the diaphragm vs clindamycin (anaerobic infections **above** diaphragm). |
| ADVERSE EFFECTS | Disulfiram-like reaction (severe flushing, tachycardia, hypotension) with alcohol; headache, metallic taste. | |

## Antimycobacterial therapy

| BACTERIUM | PROPHYLAXIS | TREATMENT |
|---|---|---|
| *M tuberculosis* | Isoniazid | **R**ifampin, **I**soniazid, **P**yrazinamide, **E**thambutol (**RIPE** for treatment) |
| *M avium–intracellulare* | Azithromycin, rifabutin | Azithromycin or clarithromycin + ethambutol<br>Can add rifabutin or ciprofloxacin |
| *M leprae* | N/A | Long-term treatment with dapsone and rifampin for tuberculoid form<br>Add clofazimine for lepromatous form |

MYCOBACTERIAL CELL




## Rifamycins

Rifampin, rifabutin, rifapentine.

| | | |
|---|---|---|
| MECHANISM | Inhibit DNA-dependent RNA polymerase. | **R**ifampin's **4 R**'s:<br>**R**NA polymerase inhibitor<br>**R**amps up microsomal cytochrome P-450<br>**R**ed/orange body fluids<br>**R**apid resistance if used alone<br>Rif**ampin ramp**s up cytochrome P-450, **but** rifa**but**in does not. |
| CLINICAL USE | *Mycobacterium tuberculosis*; delay resistance to dapsone when used for leprosy. Used for meningococcal prophylaxis and chemoprophylaxis in contacts of children with *H influenzae* type b. | |
| ADVERSE EFFECTS | Minor hepatotoxicity and drug interactions (↑ cytochrome P-450); orange body fluids (nonhazardous side effect). Rifabutin favored over rifampin in patients with HIV infection due to less cytochrome P-450 stimulation. | |
| MECHANISM OF RESISTANCE | Mutations reduce drug binding to RNA polymerase. Monotherapy rapidly leads to resistance. | |

### Isoniazid

| | | |
|---|---|---|
| MECHANISM | ↓ synthesis of mycolic acids. Bacterial catalase-peroxidase (encoded by KatG) needed to convert INH to active metabolite. | |
| CLINICAL USE | *Mycobacterium tuberculosis*. The only agent used as solo prophylaxis against TB. Also used as monotherapy for latent TB. | Different INH half-lives in fast vs slow acetylators. |
| ADVERSE EFFECTS | Hepatotoxicity, cytochrome P-450 inhibition, drug-induced SLE, anion gap metabolic acidosis, vitamin $B_6$ deficiency (peripheral neuropathy, sideroblastic anemia), seizures (in high doses, refractory to benzodiazepines). Administer with pyridoxine ($B_6$). | **INH I**njures **N**eurons and **H**epatocytes. |
| MECHANISM OF RESISTANCE | Mutations leading to underexpression of KatG. | |

### Pyrazinamide

| | |
|---|---|
| MECHANISM | Mechanism uncertain. Pyrazinamide is a prodrug that is converted to the active compound pyrazinoic acid. Works best at acidic pH (eg, in host phagolysosomes). |
| CLINICAL USE | *Mycobacterium tuberculosis*. |
| ADVERSE EFFECTS | Hyperuricemia, hepatotoxicity. |

### Ethambutol

| | |
|---|---|
| MECHANISM | ↓ carbohydrate polymerization of mycobacterium cell wall by blocking arabinosyltransferase. |
| CLINICAL USE | *Mycobacterium tuberculosis*. |
| ADVERSE EFFECTS | **Optic** neuropathy (red-green color blindness, usually reversible). Pronounce "**eye**thambutol." |

### Streptomycin

| | |
|---|---|
| MECHANISM | Interferes with 30S component of ribosome. |
| CLINICAL USE | *Mycobacterium tuberculosis* (2nd line). |
| ADVERSE EFFECTS | Tinnitus, vertigo, ataxia, nephrotoxicity. |

## Antimicrobial prophylaxis

| CLINICAL SCENARIO | MEDICATION |
|---|---|
| Exposure to meningococcal infection | Ceftriaxone, ciprofloxacin, or rifampin |
| High risk for endocarditis and undergoing surgical or dental procedures | Amoxicillin |
| History of recurrent UTIs | TMP-SMX |
| Malaria prophylaxis for travelers | Atovaquone-proguanil, mefloquine, doxycycline, primaquine, or chloroquine (for areas with sensitive species) |
| Pregnant patients carrying group B strep | Intrapartum penicillin G or ampicillin |
| Prevention of gonococcal conjunctivitis in newborn | Erythromycin ointment on eyes |
| Prevention of postsurgical infection due to *S aureus* | Cefazolin; vancomycin if ⊕ for MRSA |
| Prophylaxis of strep pharyngitis in child with prior rheumatic fever | Benzathine penicillin G or oral penicillin V |

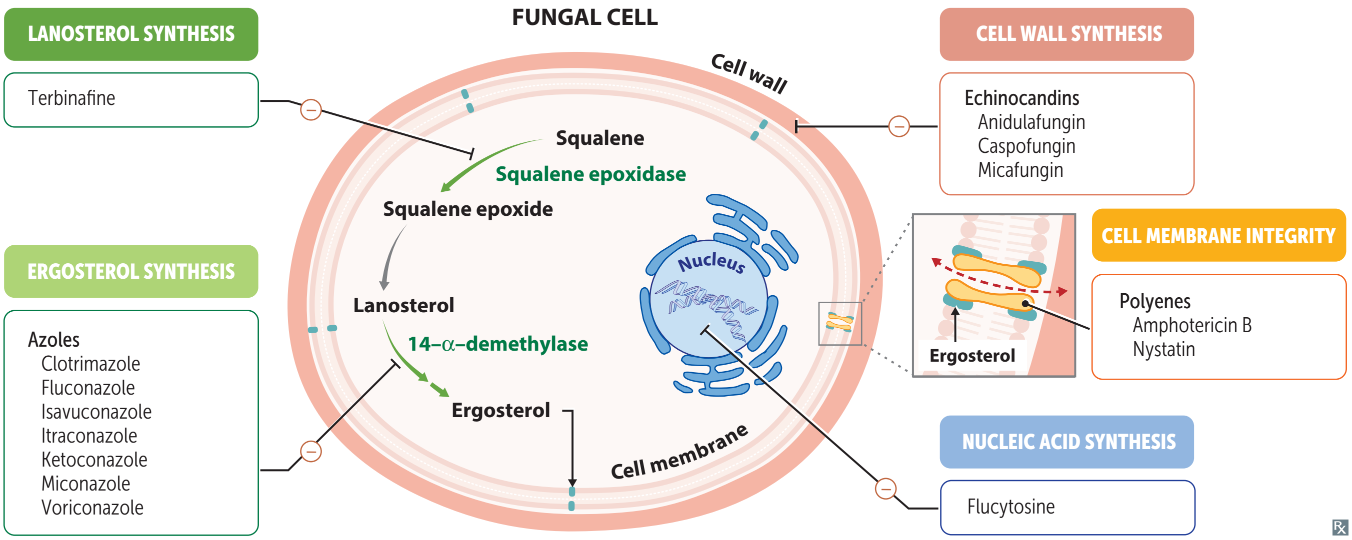
## Prophylaxis in HIV infection/AIDS

| CELL COUNT | PROPHYLAXIS | INFECTION |
|---|---|---|
| CD4 < 200 cells/mm$^3$ | TMP-SMX | *Pneumocystis* pneumonia |
| CD4 < 100 cells/mm$^3$ | TMP-SMX | *Pneumocystis* pneumonia and toxoplasmosis |

## Treatment of highly resistant bacteria

MRSA: vancomycin, daptomycin, linezolid, tigecycline, ceftaroline, doxycycline.
VRE: daptomycin, linezolid, tigecycline, and streptogramins (quinupristin, dalfopristin).
Multidrug-resistant *P aeruginosa*, multidrug-resistant *Acinetobacter baumannii:* polymyxins B and E (colistin).

## Antifungal therapy



## Amphotericin B

| | | |
|---|---|---|
| MECHANISM | Binds ergosterol (unique to fungi); forms membrane pores that allow leakage of electrolytes. | Amphotericin "tears" holes in the fungal membrane by forming pores. |
| CLINICAL USE | Serious, systemic mycoses. *Cryptococcus* (amphotericin B +/– flucytosine for cryptococcal meningitis), *Blastomyces*, *Coccidioides*, *Histoplasma*, *Candida*, *Mucor*. Intrathecally for coccidioidal meningitis. | Supplement $K^+$ and $Mg^{2+}$ because of altered renal tubule permeability. |
| ADVERSE EFFECTS | Fever/chills ("shake and bake"), hypotension, nephrotoxicity, arrhythmias, anemia, IV phlebitis ("amphoterrible"). | Hydration ↓ nephrotoxicity. Liposomal amphotericin ↓ toxicity. |

## Nystatin

| | |
|---|---|
| MECHANISM | Same as amphotericin B. Topical use only as too toxic for systemic use. |
| CLINICAL USE | "Swish and swallow" for oral candidiasis (thrush); topical for diaper rash or vaginal candidiasis. |

## Flucytosine

| | |
|---|---|
| MECHANISM | Inhibits DNA and RNA biosynthesis by conversion to 5-fluorouracil by cytosine deaminase. |
| CLINICAL USE | Systemic fungal infections (especially meningitis caused by *Cryptococcus*) in combination with amphotericin B. |
| ADVERSE EFFECTS | Bone marrow suppression. |

## Azoles

Clotrimazole, fluconazole, isavuconazole, itraconazole, ketoconazole, miconazole, voriconazole.

| | |
|---|---|
| MECHANISM | Inhibit fungal sterol (ergosterol) synthesis by inhibiting the cytochrome P-450 enzyme that converts lanosterol to ergosterol. |
| CLINICAL USE | Local and less serious systemic mycoses. Fluconazole for chronic suppression of cryptococcal meningitis in people living with HIV and candidal infections of all types. Itraconazole may be used for *Blastomyces*, *Coccidioides*, *Histoplasma*, *Sporothrix schenckii*. Clotrimazole and miconazole for topical fungal infections. Voriconazole for *Aspergillus* and some *Candida*. Isavuconazole for serious *Aspergillus* and *Mucor* infections. |
| ADVERSE EFFECTS | Testosterone synthesis inhibition (gynecomastia, especially with ketoconazole), liver dysfunction (inhibits cytochrome P-450). |

## Terbinafine

| | |
|---|---|
| MECHANISM | Inhibits the fungal enzyme squalene epoxidase. |
| CLINICAL USE | Dermatophytoses (especially onychomycosis—fungal infection of finger or toe nails). |
| ADVERSE EFFECTS | GI upset, headaches, hepatotoxicity, taste disturbance. |

| **Echinocandins** | Anidulafungin, caspofungin, micafungin. |
|---|---|
| MECHANISM | Inhibit cell wall synthesis by inhibiting synthesis of β-glucan. |
| CLINICAL USE | Invasive aspergillosis, *Candida*. |
| ADVERSE EFFECTS | GI upset, flushing (by histamine release). |

| **Griseofulvin** | |
|---|---|
| MECHANISM | Interferes with microtubule function; disrupts mitosis. Deposits in keratin-containing tissues (eg, nails). |
| CLINICAL USE | Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm). |
| ADVERSE EFFECTS | Teratogenic, carcinogenic, confusion, headaches, disulfiram-like reaction, ↑ cytochrome P-450 and warfarin metabolism. |

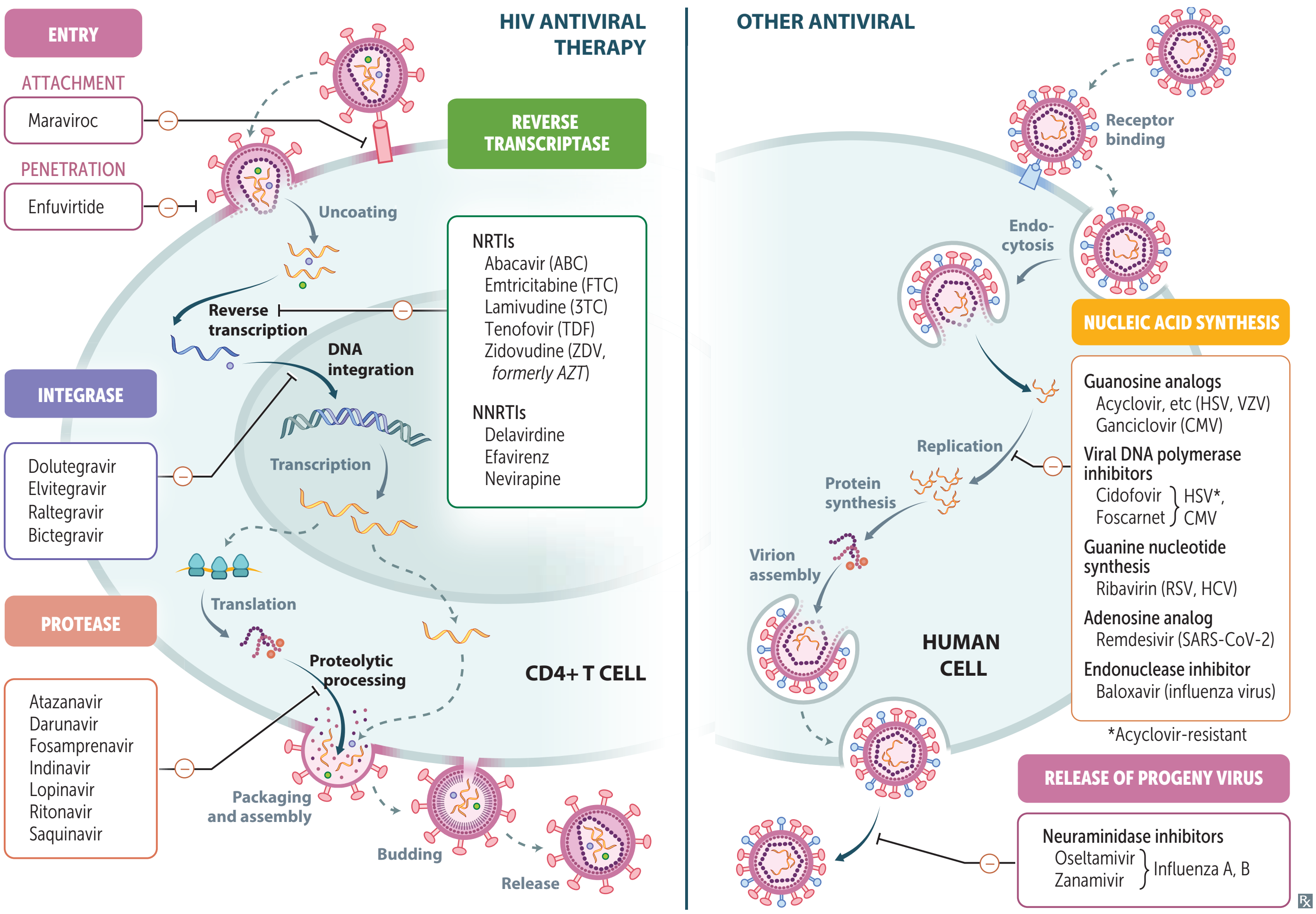
| **Antiprotozoal therapy** | Pyrimethamine (toxoplasmosis), suramin and melarsoprol (*Trypanosoma brucei*), nifurtimox (*T cruzi*), sodium stibogluconate (leishmaniasis). |
|---|---|

| **Anti-mite/louse therapy** | Permethrin, malathion (acetylcholinesterase inhibitor), topical or oral ivermectin. Used to treat scabies (*Sarcoptes scabiei*) and lice (*Pediculus* and *Pthirus*). |
|---|---|

| **Chloroquine** | |
|---|---|
| MECHANISM | Blocks detoxification of heme into hemozoin. Heme accumulates and is toxic to plasmodia. |
| CLINICAL USE | Treatment of plasmodial species other than *P falciparum* (frequency of resistance in *P falciparum* is too high). Resistance due to membrane pump that ↓ intracellular concentration of drug. Treat *P falciparum* with artemether/lumefantrine or atovaquone/proguanil. For life-threatening malaria, use quinidine in US (quinine elsewhere) or artesunate. |
| ADVERSE EFFECTS | Retinopathy; pruritus (especially in dark-skinned individuals). |

| **Antihelminthic therapy** | Pyrantel pamoate, ivermectin, mebendazole (microtubule inhibitor to treat "bendy worms"), praziquantel (↑ $Ca^{2+}$ permeability, ↑ vacuolization), diethylcarbamazine. |
|---|---|

## Antiviral therapy




### Oseltamivir, zanamivir

| | |
|---|---|
| MECHANISM | Inhibit influenza neuraminidase → ↓ release of progeny virus. |
| CLINICAL USE | Treatment and prevention of influenza A and B. Beginning therapy within 48 hours of symptom onset may shorten duration of illness. |

### Baloxavir

| | |
|---|---|
| MECHANISM | Inhibits the “cap snatching” endonuclease activity of the influenza virus RNA polymerase → ↓ viral replication. |
| CLINICAL USE | Treatment within 48 hours of symptom onset shortens duration of illness. |

### Remdesivir

| | |
|---|---|
| MECHANISM | Prodrug of an ATP analog. The active metabolite inhibits viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN) → ↓ viral RNA production. |
| CLINICAL USE | Recently approved for treatment of COVID-19 requiring hospitalization. |

## Acyclovir, famciclovir, valacyclovir

| | |
|---|---|
| MECHANISM | Guanosine analogs. Monophosphorylated by HSV/VZV thymidine kinase and not phosphorylated in uninfected cells → few adverse effects. Triphosphate formed by cellular enzymes. Preferentially inhibit viral DNA polymerase by chain termination. |
| CLINICAL USE | HSV and VZV. Weak activity against EBV. No activity against CMV. Used for HSV-induced mucocutaneous and genital lesions as well as for encephalitis. Prophylaxis in patients who are immunocompromised. No effect on latent forms of HSV and VZV. Valacyclovir, a prodrug of acyclovir, has better oral bioavailability.<br>For herpes zoster, use famciclovir. |
| ADVERSE EFFECTS | Obstructive crystalline nephropathy and acute kidney injury if not adequately hydrated. |
| MECHANISM OF RESISTANCE | Mutated viral thymidine kinase. |

## Ganciclovir

| | |
|---|---|
| MECHANISM | Guanosine analog. 5′-monophosphate formed by a CMV viral kinase. Triphosphate formed by cellular kinases. Preferentially inhibits viral DNA polymerase. |
| CLINICAL USE | CMV, especially in patients who are immunocompromised. Valganciclovir, a prodrug of ganciclovir, has better oral bioavailability. |
| ADVERSE EFFECTS | Bone marrow suppression (leukopenia, neutropenia, thrombocytopenia), renal toxicity. More toxic to host enzymes than acyclovir. |
| MECHANISM OF RESISTANCE | Mutated viral kinase. |

## Foscarnet

| | | |
|---|---|---|
| MECHANISM | Viral DNA/RNA polymerase inhibitor and HIV reverse transcriptase inhibitor. Binds to pyrophosphate-binding site of enzyme. Does not require any kinase activation. | **Fos**carnet = pyro**fos**phate analog. |
| CLINICAL USE | CMV retinitis in immunocompromised patients when ganciclovir fails; acyclovir-resistant HSV. | |
| ADVERSE EFFECTS | Nephrotoxicity, electrolyte abnormalities (hypo- or hypercalcemia, hypo- or hyperphosphatemia, hypokalemia, hypomagnesemia) can lead to seizures. | |
| MECHANISM OF RESISTANCE | Mutated DNA polymerase. | |

## Cidofovir

| | |
|---|---|
| MECHANISM | Preferentially inhibits viral DNA polymerase. Does not require phosphorylation by viral kinase. |
| CLINICAL USE | CMV retinitis in immunocompromised patients; acyclovir-resistant HSV. Long half-life. |
| ADVERSE EFFECTS | Nephrotoxicity (coadminister with probenecid and IV saline to ↓ toxicity). |

**HIV therapy**

Antiretroviral therapy (ART): often initiated at the time of HIV diagnosis.
Strongest indication for use with patients presenting with AIDS-defining illness, low CD4+ cell counts (< 500 cells/mm$^3$), or high viral load. Regimen consists of 3 drugs to prevent resistance: 2 NRTIs and preferably an integrase inhibitor.
Most ARTs are active against both HIV-1 and HIV-2 (exceptions: NNRTIs and enfuvirtide not effective against HIV-2).

| DRUG | MECHANISM | TOXICITY |
|---|---|---|
| **NRTIs** | | |
| Abacavir (ABC)<br>Emtricitabine (FTC)<br>Lamivudine (3TC)<br>Tenofovir (TDF)<br>Zidovudine (ZDV, formerly AZT) | Competitively inhibit nucleotide binding to reverse transcriptase and terminate the DNA chain (lack a 3′ OH group). **T**enofovir is a nucleo**T**ide; the others are nucleosides. All need to be phosphorylated to be active.<br>ZDV can be used for general prophylaxis and during pregnancy to ↓ risk of fetal transmission.<br>Ha**ve you dined** (**vudine**) with my **nuclear** (**nucleo**sides) family? | Bone marrow suppression (can be reversed with granulocyte colony-stimulating factor [G-CSF] and erythropoietin), peripheral neuropathy, lactic acidosis (nucleosides), anemia (ZDV).<br>Abacavir contraindicated if patient has HLA-B*5701 mutation due to ↑ risk of hypersensitivity. |
| **NNRTIs** | | |
| Delavirdine<br>Efavirenz<br>Nevirapine | Bind to reverse transcriptase at site different from NRTIs. Do not require phosphorylation to be active or compete with nucleotides. | Rash and hepatotoxicity are common to all NNRTIs. Vivid dreams and CNS symptoms are common with efavirenz. |
| **Integrase inhibitors** | | |
| Bictegravir<br>Dolutegravir<br>Elvitegravir<br>Raltegravir | Inhibits HIV genome integration into host cell chromosome by reversibly inhibiting HIV integrase. | ↑ creatine kinase. |
| **Protease inhibitors** | | |
| Atazanavir<br>Darunavir<br>Lopinavir<br>Ritonavir | Assembly of virions depends on HIV-1 protease (*pol* gene), which cleaves the polypeptide products of HIV mRNA into their functional parts. Thus, protease inhibitors prevent maturation of new viruses.<br>Ritonavir can "boost" other drug concentrations by inhibiting cytochrome P-450.<br>**Navir** (never) **tease** a **protease**. | Hyperglycemia, GI intolerance (nausea, diarrhea), lipodystrophy (Cushing-like syndrome).<br>Rifampin (potent CYP/UGT inducer) reduces protease inhibitor concentrations; use rifabutin instead. |
| **Entry inhibitors** | | |
| Enfuvirtide | Binds gp41, inhibiting viral entry. | Skin reaction at injection sites.<br>En**fu**virtide inhibits **fu**sion. |
| Maraviroc | Binds CCR-5 on surface of T cells/monocytes, inhibiting interaction with gp120. | Maravir**oc** inhibits d**oc**king. |

## Hepatitis C therapy

Chronic HCV infection treated with multidrug therapy that targets specific steps within HCV replication cycle (HCV-encoded proteins). Examples of drugs are provided.

| DRUG | MECHANISM | TOXICITY |
|---|---|---|
| **NS5A inhibitors** | | |
| Ledipasvir<br>Ombitasvir<br>Velpatasvir | Inhibits NS5A, a viral phosphoprotein that plays a key role in RNA replication<br>Exact mechanism unknown | Headache, diarrhea |
| **NS5B inhibitors** | | |
| Sofosbuvir<br>Dasabuvir | Inhibits NS5B, an RNA-dependent RNA polymerase acting as a chain terminator<br>Prevents viral RNA replication | Fatigue, headache |
| **NS3/4A inhibitors** | | |
| Grazoprevir<br>Simeprevir | Inhibits NS3/4A, a viral protease, preventing viral replication | Grazoprevir: headache, fatigue<br>Simeprevir: photosensitivity reactions, rash |
| **Alternative drugs** | | |
| Ribavirin | Inhibits synthesis of guanine nucleotides by competitively inhibiting IMP dehydrogenase<br>Used as adjunct in cases refractory to newer medications | Hemolytic anemia, severe teratogen |

## Disinfection and sterilization

Goals include the reduction of pathogenic organism counts to safe levels (disinfection) and the inactivation of all microbes including spores (sterilization).

**Chlorine** and **heat** are sporicidal.

| | |
|---|---|
| **Autoclave** | Pressurized steam at > 120°C. Sporicidal. May not reliably inactivate prions. |
| **Alcohols** | Denature proteins and disrupt cell membranes. Not sporicidal. |
| **Chlorhexidine** | Disrupts cell membranes and coagulates intracellular components. |
| **Chlorine** | Oxidizes and denatures proteins. Sporicidal. |
| **Ethylene oxide** | Alkylating agent. Sporicidal. |
| **Hydrogen peroxide** | Free radical oxidation. Sporicidal. |
| **Iodine and iodophors** | Halogenation of DNA, RNA, and proteins. May be sporicidal. |
| **Quaternary amines** | Impair permeability of cell membranes. Not sporicidal. |

## Antimicrobials to avoid in pregnancy

| ANTIMICROBIAL | ADVERSE EFFECT |
|---|---|
| **S**ulfonamides | Kernicterus |
| **A**minoglycosides | Ototoxicity |
| **F**luoroquinolones | Cartilage damage |
| **C**larithromycin | Embryotoxic |
| **T**etracyclines | Discolored teeth, inhibition of bone growth |
| **R**ibavirin | Teratogenic |
| **G**riseofulvin | Teratogenic |
| **C**hloramphenicol | Gray baby syndrome |

**Saf**e **c**hildren **t**ake **r**eally **g**ood **c**are.

HIGH-YIELD PRINCIPLES IN

# Pathology

*"Digressions, objections, delight in mockery, carefree mistrust are signs of health; everything unconditional belongs in pathology."*

—Friedrich Nietzsche

*"You cannot separate passion from pathology any more than you can separate a person's spirit from his body."*

—Richard Selzer

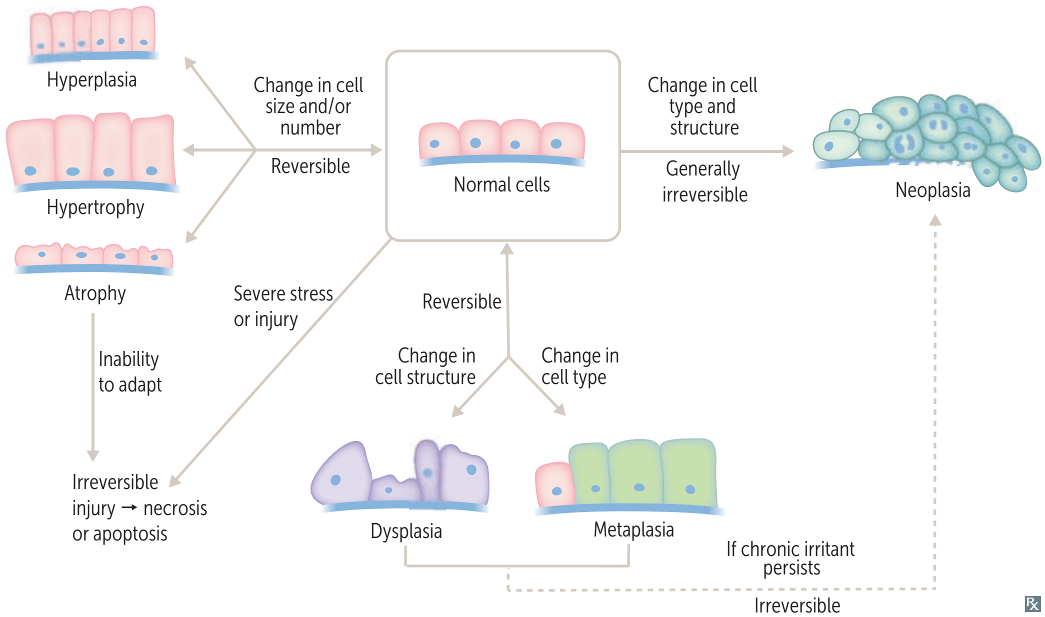
*"My business is not prognosis, but diagnosis. I am not engaged in therapeutics, but in pathology."*

—H.L. Mencken

The fundamental principles of pathology are key to understanding diseases in all organ systems. Major topics such as inflammation and neoplasia appear frequently in questions across different organ systems, and such topics are definitely high yield. For example, the concepts of cell injury and inflammation are key to understanding the inflammatory response that follows myocardial infarction, a very common subject of board questions. Similarly, a familiarity with the early cellular changes that culminate in the development of neoplasias—for example, esophageal or colon cancer—is critical. Finally, make sure you recognize the major tumor-associated genes and are comfortable with key cancer concepts such as tumor staging and metastasis.

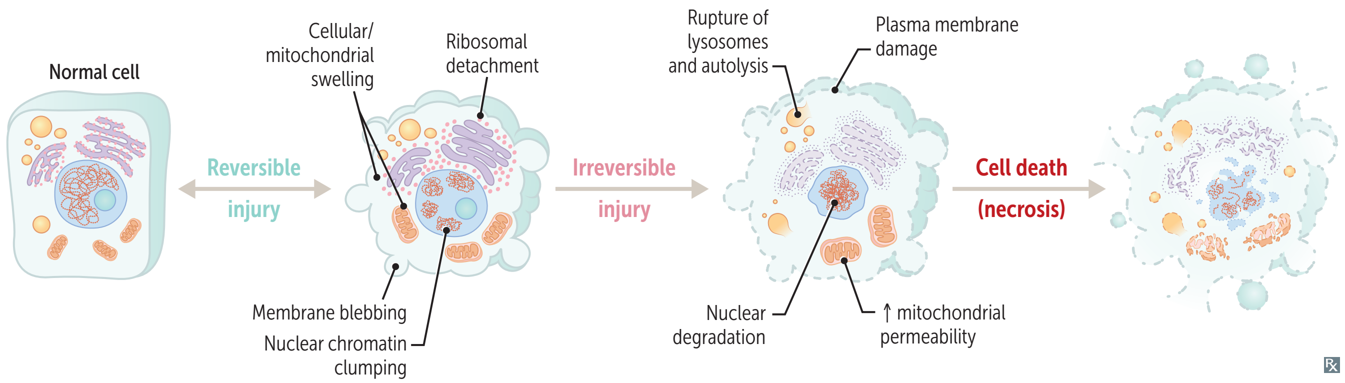
## ▶ PATHOLOGY—CELLULAR INJURY

| | |
|---|---|
| **Cellular adaptations** | Reversible changes that can be physiologic (eg, uterine enlargement during pregnancy) or pathologic (eg, myocardial hypertrophy 2° to systemic HTN). If stress is excessive or persistent, adaptations can progress to cell injury (eg, significant LV hypertrophy → injury to myofibrils → HF). |
| **Hypertrophy** | ↑ structural proteins and organelles → ↑ in size of cells. Example: cardiac hypertrophy. |
| **Hyperplasia** | Controlled proliferation of stem cells and differentiated cells → ↑ in number of cells (eg, benign prostatic hyperplasia). Excessive stimulation → pathologic hyperplasia (eg, endometrial hyperplasia), which may progress to dysplasia and cancer. |
| **Atrophy** | ↓ in tissue mass due to ↓ in size (↑ cytoskeleton degradation via ubiquitin-proteasome pathway and autophagy; ↓ protein synthesis) and/or number of cells (apoptosis). Causes include disuse, denervation, loss of blood supply, loss of hormonal stimulation, poor nutrition. |
| **Metaplasia** | Reprogramming of stem cells → replacement of one cell type by another that can adapt to a new stress. Usually due to exposure to an irritant, such as gastric acid (→ Barrett esophagus) or tobacco smoke (→ respiratory ciliated columnar epithelium replaced by stratified squamous epithelium). May progress to dysplasia → malignant transformation with persistent insult (eg, Barrett esophagus → esophageal adenocarcinoma). Metaplasia of connective tissue can also occur (eg, myositis ossificans, the formation of bone within muscle after trauma). |
| **Dysplasia** | Disordered, precancerous epithelial cell growth; not considered a true adaptive response. Characterized by loss of uniformity of cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, ↑ nuclear:cytoplasmic ratio and clumped chromatin). Mild and moderate dysplasias (ie, do not involve entire thickness of epithelium) may regress with alleviation of inciting cause. Severe dysplasia often becomes irreversible and progresses to carcinoma in situ. Usually preceded by persistent metaplasia or pathologic hyperplasia. |



## Cell injury

| | |
|---|---|
| **Reversible cell injury** | ▪ ↓ ATP → ↓ activity of $Ca^{2+}$ and $Na^+/K^+$ pumps → cellular swelling (earliest morphologic manifestation), mitochondrial swelling<br>▪ Ribosomal/polysomal detachment → ↓ protein synthesis<br>▪ Plasma membrane changes (eg, blebbing)<br>▪ Nuclear changes (eg, chromatin clumping)<br>▪ Rapid loss of function (eg, myocardial cells are noncontractile after 1-2 minutes of ischemia)<br>▪ Myelin figures (aggregation of peroxidized lipids) |
| **Irreversible cell injury** | ▪ Breakdown of plasma membrane → cytosolic enzymes (eg, troponin) leak outside of cell, influx of $Ca^{2+}$ → activation of degradative enzymes<br>▪ Mitochondrial damage/dysfunction → loss of electron transport chain → ↓ ATP<br>▪ Rupture of lysosomes → autolysis<br>▪ Nuclear degradation: pyknosis (nuclear condensation) → karyorrhexis (nuclear fragmentation caused by endonuclease-mediated cleavage) → karyolysis (nuclear dissolution)<br>▪ Amorphous densities/inclusions in mitochondria |



**Apoptosis**

ATP-dependent programmed cell death.

Intrinsic and extrinsic pathways; both pathways activate caspases (cytosolic proteases) → cellular breakdown including cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies, which are then phagocytosed.

Characterized by deeply eosinophilic cytoplasm and basophilic nucleus, pyknosis, and karyorrhexis.

Cell membrane typically remains intact without significant inflammation (unlike necrosis).

DNA laddering (fragments in multiples of 180 bp) is a sensitive indicator of apoptosis.

**Intrinsic (mitochondrial) pathway**

Involved in tissue remodeling in embryogenesis. Occurs when a regulating factor is withdrawn from a proliferating cell population (eg, ↓ IL-2 after a completed immunologic reaction → apoptosis of proliferating effector cells). Also occurs after exposure to injurious stimuli (eg, radiation, toxins, hypoxia).

Regulated by Bcl-2 family of proteins. **BA**X and **BA**K are proapoptotic (**BA**d for survival), while **Bcl**-2 and **Bcl**-xL are antiapoptotic (**B**e **c**lever, **l**ive).

BAX and BAK form pores in the mitochondrial membrane → release of cytochrome C from inner mitochondrial membrane into the cytoplasm → activation of caspases.

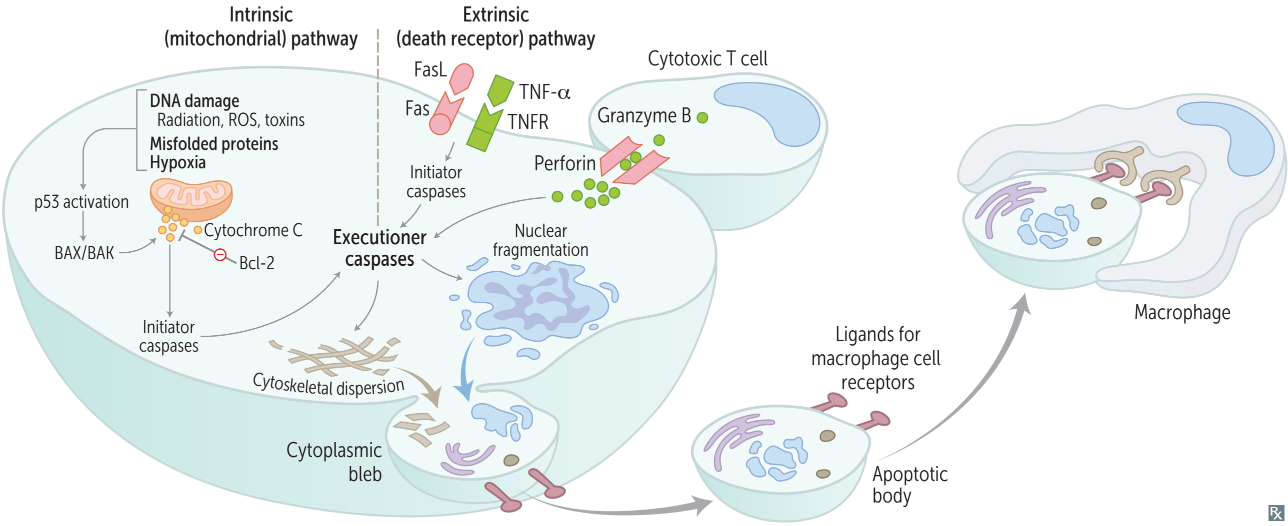
Bcl-2 keeps the mitochondrial membrane impermeable, thereby preventing cytochrome C release. Bcl-2 overexpression (eg, follicular lymphoma t[14;18]) → ↓ caspase activation → tumorigenesis.

**Extrinsic (death receptor) pathway**

2 pathways:
- Ligand receptor interactions (FasL binding to Fas [CD95] or TNF-α binding to its receptor)
- Immune cell (cytotoxic T-cell release of perforin and granzyme B)

Fas-FasL interaction is necessary in thymic medullary negative selection.

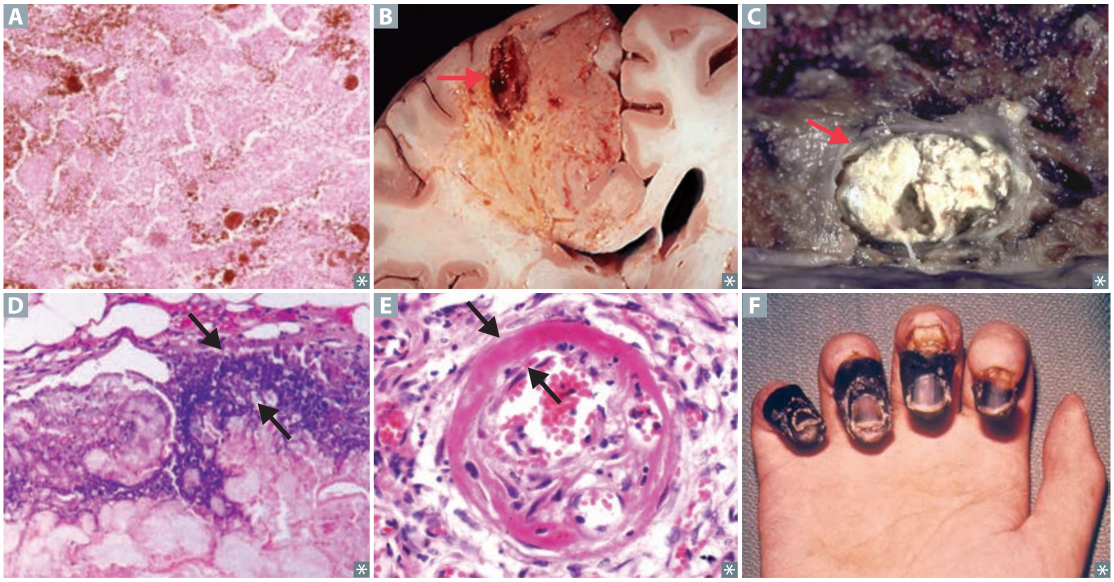
Defective Fas-FasL interactions → failure of clonal deletion → ↑ numbers of self-reacting lymphocytes → autoimmune lymphoproliferative syndrome.



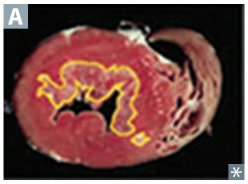
**Necrosis**

Exogenous injury → plasma membrane damage → cell undergoes enzymatic degradation and protein denaturation, intracellular components leak → local inflammatory reaction (unlike apoptosis).

| TYPE | SEEN IN | DUE TO | HISTOLOGY |
|---|---|---|---|
| **Coagulative** | Ischemia/infarcts in most tissues (except brain) | Ischemia or infarction; injury denatures enzymes → proteolysis blocked | Preserved cellular architecture (cell outlines seen), but nuclei disappear; ↑ cytoplasmic binding of eosin stain (→ ↑ eosinophilia; red/pink color) A |
| **Liquefactive** | Bacterial abscesses, brain infarcts | Neutrophils release lysosomal enzymes that digest the tissue B | Early: cellular debris and macrophages<br>Late: cystic spaces and cavitation (brain)<br>Neutrophils and cell debris seen with bacterial infection |
| **Caseous** | TB, systemic fungi (eg, *Histoplasma capsulatum*), *Nocardia* | Macrophages wall off the infecting microorganism → granular debris | Cheese-like gross appearance C<br>Fragmented cells and debris surrounded by lymphocytes and macrophages (granuloma) |
| **Fat** | Enzymatic: acute pancreatitis (saponification of peripancreatic fat)<br>Nonenzymatic: traumatic (eg, injury to breast tissue) | Damaged pancreatic cells release lipase, which breaks down triglycerides; liberated fatty acids bind calcium → saponification (chalky-white appearance) | Outlines of dead fat cells without peripheral nuclei; saponification of fat (combined with $Ca^{2+}$) appears dark blue on H&E stain D |
| **Fibrinoid** | Immune vascular reactions (eg, PAN)<br>Nonimmune vascular reactions (eg, hypertensive emergency, preeclampsia) | Immune complex deposition (type III hypersensitivity reaction) and/or plasma protein (eg, fibrin) leakage from damaged vessel | Vessel walls contain eosinophilic layer of proteinaceous material E |
| **Gangrenous** | Distal extremity and GI tract, after chronic ischemia | Dry: ischemia F | Coagulative |
| | | Wet: superinfection | Liquefactive superimposed on coagulative |



## Ischemia




Inadequate blood supply to meet demand. Mechanisms include ↓ arterial perfusion (eg, atherosclerosis), ↓ venous drainage (eg, testicular torsion, Budd-Chiari syndrome), shock.

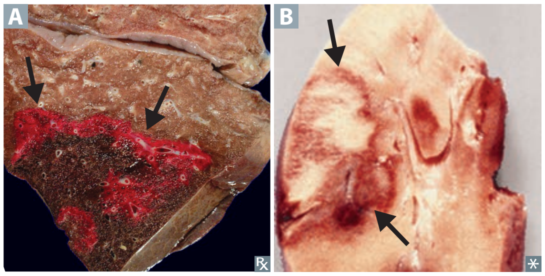
Regions most vulnerable to hypoxia/ischemia and subsequent infarction:

| ORGAN | REGION |
|---|---|
| Brain | ACA/MCA/PCA boundary areas[a,b] |
| Heart | Subendocardium of LV (yellow lines in A outline a subendocardial infarction) |
| Kidney | Straight segment of proximal tubule (medulla)<br>Thick ascending limb (medulla) |
| Liver | Area around central vein (zone III) |
| Colon | Splenic flexure (Griffith point),[a] rectosigmoid junction (Sudeck point)[a] |

[a]Watershed areas (border zones) receive blood supply from most distal branches of 2 arteries with limited collateral vascularity. These areas are susceptible to ischemia from hypoperfusion.

[b]Neurons most vulnerable to hypoxic-ischemic insults include Purkinje cells of the cerebellum and pyramidal cells of the hippocampus and neocortex (zones 3, 5, 6).

## Types of infarcts




### Red infarct

Occurs in venous occlusion and tissues with multiple blood supplies (eg, liver, lung A, intestine, testes), and with reperfusion (eg, after angioplasty). **Re**perfusion injury is due to damage by free radicals.

### Pale infarct

Occurs in solid organs with a single (end-arterial) blood supply (eg, heart, kidney B).

## Free radical injury

Free radicals damage cells via membrane lipid peroxidation, protein modification, DNA breakage. Initiated via radiation exposure (eg, cancer therapy), metabolism of drugs (phase I), redox reactions, nitric oxide (eg, inflammation), transition metals, WBC (eg, neutrophils, macrophages) oxidative burst.

Free radicals can be eliminated by scavenging enzymes (eg, catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (eg, vitamins A, C, E), and certain metal carrier proteins (eg, transferrin, ceruloplasmin).

Examples:

- Oxygen toxicity: retinopathy of prematurity (abnormal vascularization), bronchopulmonary dysplasia, reperfusion injury after thrombolytic therapy
- Drug/chemical toxicity: acetaminophen overdose (hepatotoxicity), carbon tetrachloride (converted by cytochrome P-450 into $CCl_3$ free radical → fatty liver [cell injury → ↓ apolipoprotein synthesis → fatty change], centrilobular necrosis)
- Metal storage diseases: hemochromatosis (iron) and Wilson disease (copper)

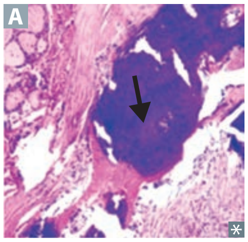
**Ionizing radiation toxicity**

Ionization radiation induces cellular and DNA damage directly (via photons or particles) and indirectly (via generation of reactive oxygen species) → progressive inflammation and tissue damage. Rapidly regenerating tissues (eg, skin epithelia, bone marrow, GI tract, GU tract, gonads) more susceptible to injury. Can cause both acute and delayed (late) toxicities.

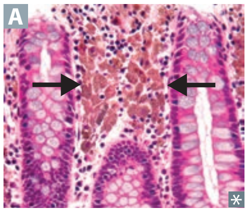
| RADIATION TOXICITY | SYSTEM | DISEASE/CLINICAL MANIFESTATION |
|---|---|---|
| Full exposure | | |
| **Acute radiation syndrome** | Skin | Hair loss, erythema, desquamation, ulcers/necrosis |
| | Hematopoietic | Myelosuppression |
| | Gastrointestinal | Mucosal denudation, inflammation, edema → abdominal pain, diarrhea, GI bleeding, nausea, vomiting, stomatitis |
| | Neurovascular | Papilledema, seizures, ataxia, impaired reflexes, cognitive deficits |
| Partial exposure | | |
| **Acute local toxicity** | Skin, gonads, eye | Blisters, sterility, ↓ spermatogenesis, cataracts |
| Late complication | | |
| **Radiation-induced fibrosis** | Skin, subcutaneous tissue | Induration, thickening, loss of elasticity, shrinkage, lymphedema |
| | Lung | Pulmonary fibrosis |
| | Head and neck | Trismus, mucosal fibrosis, ulceration, fistulae |
| | Gastrointestinal | Obstruction, ulcerations, fistulae |
| | Genitourinary | Ureteral and urethral stenosis, fibrotic bladder constriction → obstructive uropathy; fibrosis of ovaries, vulva, vagina; azoospermia |
| **Radiation-related malignancies** | Thyroid | Papillary thyroid carcinoma |
| | Hematopoietic | Myelodysplastic syndromes, lymphomas, leukemias (eg, CML, AML, ALL) |
| | Skin | Angiosarcoma |
| | Bone | Osteosarcoma |
| | Others | Solid tumors (eg, breast, ovarian, lung) |

## Types of calcification

Calcium deposits appear deeply basophilic (arrow in A) on H&E stain.

| | Dystrophic calcification | Metastatic calcification |
|---|---|---|
| $Ca^{2+}$ DEPOSITION | In abnormal (diseased) tissues | In normal tissues |
| EXTENT | Tends to be localized (eg, calcific aortic stenosis) | Widespread (ie, diffuse, metastatic) |
| ASSOCIATED CONDITIONS  | TB (lung and pericardium) and other granulomatous infections, liquefactive necrosis of chronic abscesses, fat necrosis, infarcts, thrombi, schistosomiasis, congenital CMV, toxoplasmosis, rubella, psammoma bodies, CREST syndrome, atherosclerotic plaques can become calcified | Predominantly in interstitial tissues of kidney, lung, and gastric mucosa (these tissues lose acid quickly; ↑ pH favors $Ca^{2+}$ deposition)<br>Nephrocalcinosis of collecting ducts may lead to nephrogenic diabetes insipidus and renal failure |
| ETIOLOGY | 2° to injury or necrosis | 2° to hypercalcemia (eg, 1° hyperparathyroidism, sarcoidosis, hypervitaminosis D) or high calcium-phosphate product levels (eg, chronic kidney disease with 2° hyperparathyroidism, long-term dialysis, calciphylaxis, multiple myeloma) |
| SERUM $Ca^{2+}$ LEVELS | Normal | Usually abnormal |

## Lipofuscin



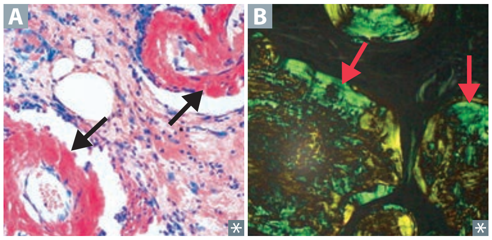
A yellow-brown "wear and tear" pigment A associated with normal aging.

Composed of polymers of lipids and phospholipids complexed with protein. May be derived through lipid peroxidation of polyunsaturated lipids of subcellular membranes.

Autopsy of elderly person will reveal deposits in heart, colon, liver, kidney, eye, and other organs.

**Amyloidosis**

Abnormal aggregation of proteins (or their fragments) into β-pleated linear sheets → insoluble fibrils → cellular damage and apoptosis. Amyloid deposits visualized by Congo red stain (red/orange on nonpolarized light [arrows in A]), (apple-green birefringence on polarized light [arrows in B]), and H&E stain (shows deposits in glomerular mesangial areas). Tubular basement membranes are enlarged on light microscopy.




| COMMON TYPES | FIBRIL PROTEIN | DESCRIPTION | |
|---|---|---|---|
| **Systemic** | | | |
| **Primary amyloidosis** | AL (from Ig Light chains) | Seen in plasma cell disorders (eg, multiple myeloma) | Manifestations include:<br>▪ Cardiac (eg, restrictive cardiomyopathy)<br>▪ GI (eg, macroglossia, hepatomegaly)<br>▪ Renal (eg, nephrotic syndrome)<br>▪ Hematologic (eg, easy bruising, splenomegaly)<br>▪ Neurologic (eg, neuropathy)<br>▪ Musculoskeletal (eg, carpal tunnel syndrome) |
| **Secondary amyloidosis** | Serum Amyloid A (AA) | Seen in chronic inflammatory conditions, (eg, rheumatoid arthritis, IBD, familial Mediterranean fever, protracted infection) | |
| **Dialysis-related amyloidosis** | $\beta_2$-microglobulin | Seen in patients with ESRD and/or on long-term dialysis | |
| **Localized** | | | |
| **Alzheimer disease** | β-amyloid protein | Cleaved from amyloid precursor protein (APP) | |
| **Type 2 diabetes mellitus** | Islet amyloid polypeptide (IAPP) | Caused by deposition of amylin in pancreatic islets | |
| **Medullary thyroid cancer** | Calcitonin | | |
| **Isolated atrial amyloidosis** | ANP | Common in normal aging<br>↑ risk of atrial fibrillation | |
| **Systemic senile (age-related) amyloidosis** | Normal (wild-type) transthyretin (TTR) | Seen predominantly in cardiac ventricles | Cardiac dysfunction more insidious than in AL amyloidosis |
| **Hereditary** | | | |
| **Familial amyloid cardiomyopathy** | Mutated transthyretin (ATTR) | Ventricular endomyocardium deposition → restrictive cardiomyopathy, arrhythmias | 3–4% of African-Americans are carriers of a mutated allele |
| **Familial amyloid polyneuropathies** | Mutated transthyretin (ATTR) | Due to transthyretin gene mutation | |

## ▸ PATHOLOGY—INFLAMMATION

**Inflammation** Response to eliminate initial cause of cell injury, to remove necrotic cells resulting from the original insult, and to initiate tissue repair. Divided into acute and chronic. The inflammatory response itself can be harmful to the host if the reaction is excessive (eg, septic shock), prolonged (eg, persistent infections such as TB), or inappropriate (eg, autoimmune diseases such as SLE).

| SIGN | MECHANISM | MEDIATORS |
|---|---|---|
| **Cardinal signs** | | |
| **Rubor and calor** | Redness and warmth. Vasodilation (relaxation of arteriolar smooth muscle) → ↑ blood flow. | Histamine, prostaglandins, bradykinin, NO. |
| **Tumor** | Swelling. Endothelial contraction/disruption (eg, from tissue damage) → ↑ vascular permeability → leakage of protein-rich fluid from postcapillary venules into interstitial space (exudate) → ↑ interstitial oncotic pressure. | Endothelial contraction: leukotrienes ($C_4$, $D_4$, $E_4$), histamine, serotonin. |
| **Dolor** | Pain. Sensitization of sensory nerve endings. | Bradykinin, $PGE_2$, histamine. |
| **Functio laesa** | Loss of function. Inflammation impairs function (eg, inability to make fist due to hand cellulitis). | |
| **Systemic manifestations (acute-phase reaction)** | | |
| **Fever** | Pyrogens (eg, LPS) induce macrophages to release IL-1 and TNF → ↑ COX activity in perivascular cells of anterior hypothalamus → ↑ $PGE_2$ → ↑ temperature set point. | |
| **Leukocytosis** | ↑ WBC count; type of predominant cell depends on inciting agent or injury (eg, bacteria → ↑ neutrophils). | |
| **↑ plasma acute-phase reactants** | Serum concentrations significantly change in response to acute and chronic inflammation. Produced by liver. | Notably induced by IL-6. |

**Acute phase reactants** More FFiSHH Pee in the C (sea).

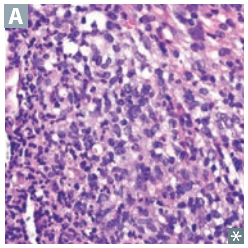
| POSITIVE (UPREGULATED) | |
|---|---|
| **Ferritin** | Binds and sequesters iron to inhibit microbial iron scavenging. |
| **Fibrinogen** | Coagulation factor; promotes endothelial repair; correlates with ESR. |
| **Serum amyloid A** | Prolonged elevation can lead to amyloidosis. |
| **Hepcidin** | ↓ iron absorption (by degrading ferroportin) and ↓ iron release (from macrophages) → anemia of chronic disease. |
| **Haptoglobin** | Binds extracellular hemoglobin, protects against oxidative stress. |
| **Procalcitonin** | Rises in bacterial infections. |
| **C-reactive protein** | Opsonin; fixes complement and facilitates phagocytosis.<br>Measured clinically as a nonspecific sign of ongoing inflammation. |
| **NEGATIVE (DOWNREGULATED)** | |
| **Albumin** | Reduction conserves amino acids for positive reactants. |
| **Transferrin** | Internalized by macrophages to sequester iron. |

**Erythrocyte sedimentation rate**

RBCs normally remain separated via ⊖ charges. Products of inflammation (eg, fibrinogen) coat RBCs → ↓ ⊖ charge → ↑ RBC aggregation. Denser RBC aggregates fall at a faster rate within a pipette tube → ↑ ESR. Often co-tested with CRP (more specific marker of inflammation).

| ↑ ESR | ↓ ESR |
|---|---|
| Most anemias | Sickle cell anemia (altered shape) |
| Infections | Polycythemia (↑ RBCs "dilute" aggregation factors) |
| Inflammation (eg, giant cell [temporal] arteritis, polymyalgia rheumatica) | HF |
| Cancer (eg, metastases, multiple myeloma) | Microcytosis |
| Renal disease (end-stage or nephrotic syndrome) | Hypofibrinogenemia |
| Pregnancy | |

**Acute inflammation**




Transient and early response to injury or infection. Characterized by neutrophils in tissue A, often with associated edema. Rapid onset (seconds to minutes) and short duration (minutes to days). Represents a reaction of the innate immune system (ie, less specific response than chronic inflammation).

STIMULI

Infections, trauma, necrosis, foreign bodies.

MEDIATORS

Toll-like receptors, arachidonic acid metabolites, neutrophils, eosinophils, antibodies (pre-existing), mast cells, basophils, complement, Hageman factor (factor XII).

Inflammasome—Cytoplasmic protein complex that recognizes products of dead cells, microbial products, and crystals (eg, uric acid crystals) → activation of IL-1 and inflammatory response.

COMPONENTS

- Vascular: vasodilation (→ ↑ blood flow and stasis) and ↑ endothelial permeability (contraction of endothelial cells opens interendothelial junctions)
- Cellular: extravasation of leukocytes (mainly neutrophils) from postcapillary venules and accumulation in the focus of injury followed by leukocyte activation

To bring cells and proteins to site of injury or infection.

Leukocyte extravasation has 4 steps: margination and rolling, adhesion, transmigration, and migration (chemoattraction).

OUTCOMES

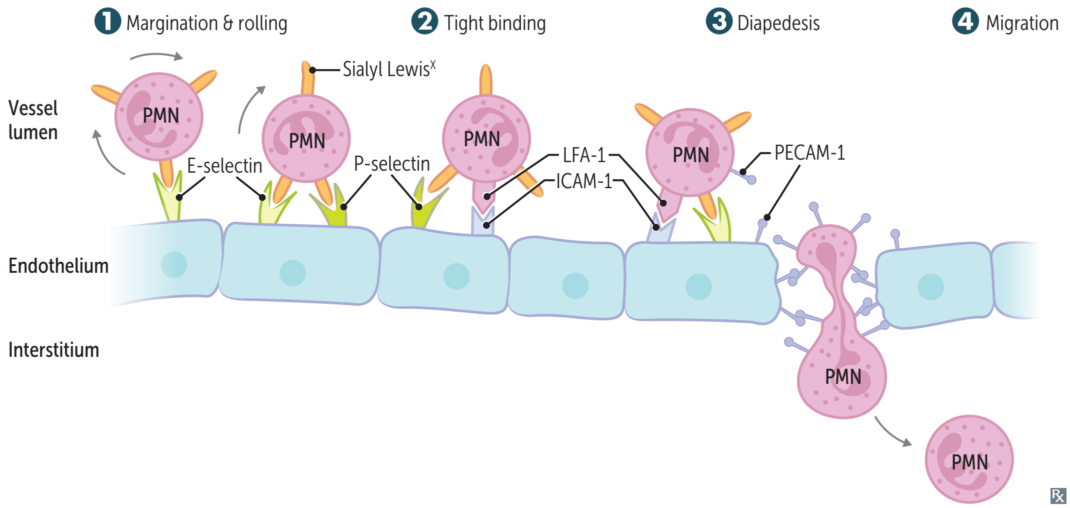
- Resolution and healing (IL-10, TGF-β)
- Persistent acute inflammation (IL-8)
- Abscess (acute inflammation walled off by fibrosis)
- Chronic inflammation (antigen presentation by macrophages and other APCs → activation of $CD4^+$ Th cells)
- Scarring

Macrophages predominate in the late stages of acute inflammation (peak 2–3 days after onset) and influence outcome by secreting cytokines.

**Leukocyte extravasation**

Extravasation predominantly occurs at postcapillary venules.

| STEP | VASCULATURE/STROMA | LEUKOCYTE |
|---|---|---|
| ❶ Margination and rolling—defective in leukocyte adhesion deficiency type 2 (↓ Sialyl Lewis$^X$) | E-selectin (upregulated by TNF and IL-1)<br>**P**-selectin (released from Weibel-**p**alade bodies)<br>GlyCAM-1, CD34 | Sialyl Lewis$^X$<br>Sialyl Lewis$^X$<br>L-selectin |
| ❷ Tight binding (adhesion)—defective in leukocyte adhesion deficiency type 1 (↓ CD18 integrin subunit) | ICAM-1 (CD54)<br>VCAM-1 (CD106) | CD11/18 integrins (LFA-1, Mac-1)<br>VLA-4 integrin |
| ❸ Dia**PE**desis (transmigration)—WBC travels between endothelial cells and exits blood vessel | **PE**CAM-1 (CD31) | **PE**CAM-1 (CD31) |
| ❹ Migration—WBC travels through interstitium to site of injury or infection guided by chemotactic signals | Chemotactic factors: C5a, IL-8, $LTB_4$, kallikrein, platelet-activating factor, *N*-formylmethionyl peptides | Various |



| | |
|---|---|
| **Chronic inflammation** | Prolonged inflammation characterized by mononuclear infiltration (macrophages, lymphocytes, plasma cells), which leads to simultaneous tissue destruction and repair (including angiogenesis and fibrosis). May be preceded by acute inflammation. |
| STIMULI | Persistent infections (eg, TB, *T pallidum*, certain fungi and viruses) → type IV hypersensitivity, autoimmune diseases, prolonged exposure to toxic agents (eg, silica) and foreign material. |
| MEDIATORS | Macrophages are the dominant cells. Interaction of macrophages and T lymphocytes → chronic inflammation.<br>▪ Th1 cells secrete IFN-γ → macrophage classical activation (proinflammatory)<br>▪ Th2 cells secrete IL-4 and IL-13 → macrophage alternative activation (repair and anti-inflammatory) |
| OUTCOMES | Scarring, amyloidosis, and neoplastic transformation (eg, chronic HCV infection → chronic inflammation → hepatocellular carcinoma; *Helicobacter pylori* infection → chronic gastritis → gastric adenocarcinoma). |

## Wound healing

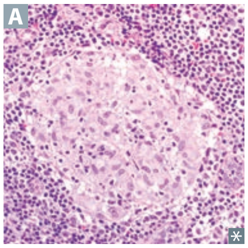
| Tissue mediators | MEDIATOR | ROLE |
|---|---|---|
| | FGF | Stimulates angiogenesis |
| | TGF-β | Angiogenesis, fibrosis |
| | VEGF | Stimulates angiogenesis |
| | PDGF | Secreted by activated platelets and macrophages<br>Induces vascular remodeling and smooth muscle cell migration<br>Stimulates fibroblast growth for collagen synthesis |
| | Metalloproteinases | Tissue remodeling |
| | EGF | Stimulates cell growth via tyrosine kinases (eg, EGFR/*ErbB1*) |

| PHASE OF WOUND HEALING | EFFECTOR CELLS | CHARACTERISTICS |
|---|---|---|
| **Inflammatory (up to 3 days after wound)** | Platelets, neutrophils, macrophages | Clot formation, ↑ vessel permeability and neutrophil migration into tissue; macrophages clear debris 2 days later |
| **Proliferative (day 3–weeks after wound)** | Fibroblasts, myofibroblasts, endothelial cells, keratinocytes, macrophages | Deposition of granulation tissue and type III collagen, angiogenesis, epithelial cell proliferation, dissolution of clot, and wound contraction (mediated by myofibroblasts)<br>Delayed second phase of wound healing in vitamin C and copper deficiency |
| **Remodeling (1 week–6+ months after wound)** | Fibroblasts | Type III collagen replaced by type I collagen, ↑ tensile strength of tissue<br>Collagenases (require zinc to function) break down type III collagen<br>Zinc deficiency → delayed wound healing |

**Granulomatous inflammation**

A pattern of chronic inflammation. Can be induced by persistent T-cell response to certain infections (eg, TB), immune-mediated diseases, and foreign bodies. Granulomas "wall off" a resistant stimulus without completely eradicating or degrading it → persistent inflammation→ fibrosis, organ damage.

HISTOLOGY



Focus of epithelioid cells (activated macrophages with abundant pink cytoplasm) surrounded by lymphocytes and multinucleated giant cells (formed by fusion of several activated macrophages). Two types:

Caseating: associated with central necrosis. Seen with infectious etiologies (eg, TB, fungal).

Noncaseating A: no central necrosis. Seen with autoimmune diseases (eg, sarcoidosis, Crohn disease).

MECHANISM

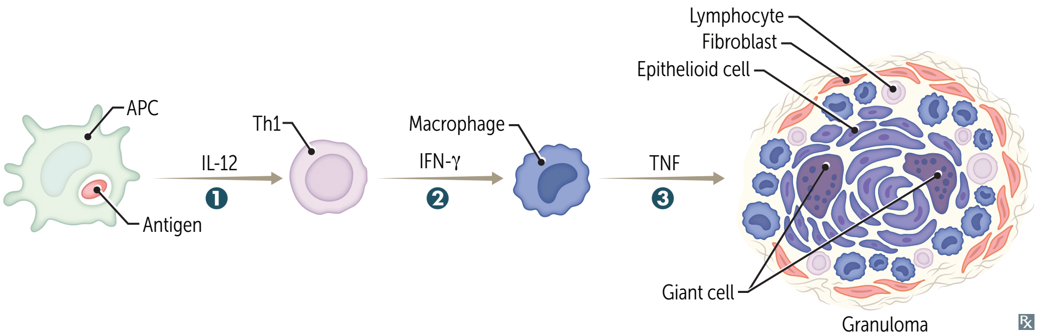
❶ APCs present antigens to CD4+ Th cells and secrete IL-12 → CD4+ Th cells differentiate into Th1 cells

❷ Th1 secretes IFN-γ → macrophage activation

❸ Macrophages ↑ cytokine secretion (eg, TNF) → formation of epithelioid macrophages and giant cells

Anti-TNF therapy can cause sequestering granulomas to break down → disseminated disease. Always test for latent TB before starting anti-TNF therapy.

Associated with hypercalcemia due to ↑ 1α-hydroxylase activity in activated macrophages, resulting in ↑ vitamin D activity.




ETIOLOGIES

| INFECTIOUS | NONINFECTIOUS |
|---|---|
| Bacterial: *Mycobacteria* (tuberculosis, leprosy), *Bartonella henselae* (cat scratch disease; stellate necrotizing granulomas), *Listeria monocytogenes* (granulomatosis infantiseptica), *Treponema pallidum* (3° syphilis) | Immune-mediated: sarcoidosis, Crohn disease, 1° biliary cholangitis, subacute (de Quervain/granulomatous) thyroiditis |
| Fungal: endemic mycoses (eg, histoplasmosis) | Vasculitis: granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, giant cell (temporal) arteritis, Takayasu arteritis |
| Parasitic: schistosomiasis | Foreign bodies: berylliosis, talcosis, hypersensitivity pneumonitis |
| | Chronic granulomatous disease |

**Scar formation** Occurs when repair cannot be accomplished by cell regeneration alone. Nonregenerated cells (2° to severe acute or chronic injury) are replaced by connective tissue. 70–80% of tensile strength regained at 3 months; little tensile strength regained thereafter. Associated with excess TGF-β.

| SCAR TYPE | Hypertrophic A | Keloid B |
|---|---|---|
| COLLAGEN SYNTHESIS | ↑ (type III collagen) | ↑↑↑ (types I and III collagen) |
| COLLAGEN ORGANIZATION | Parallel | Disorganized |
| EXTENT OF SCAR | Confined to borders of original wound | Extends beyond borders of original wound with "claw-like" projections typically on earlobes, face, upper extremities |
| RECURRENCE | Infrequent | Frequent |
| PREDISPOSITION | None | ↑ incidence in people with darker skin |

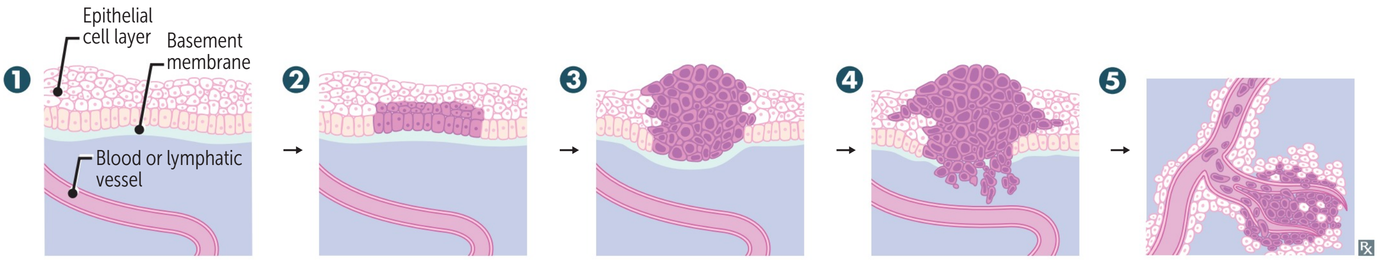
A


B

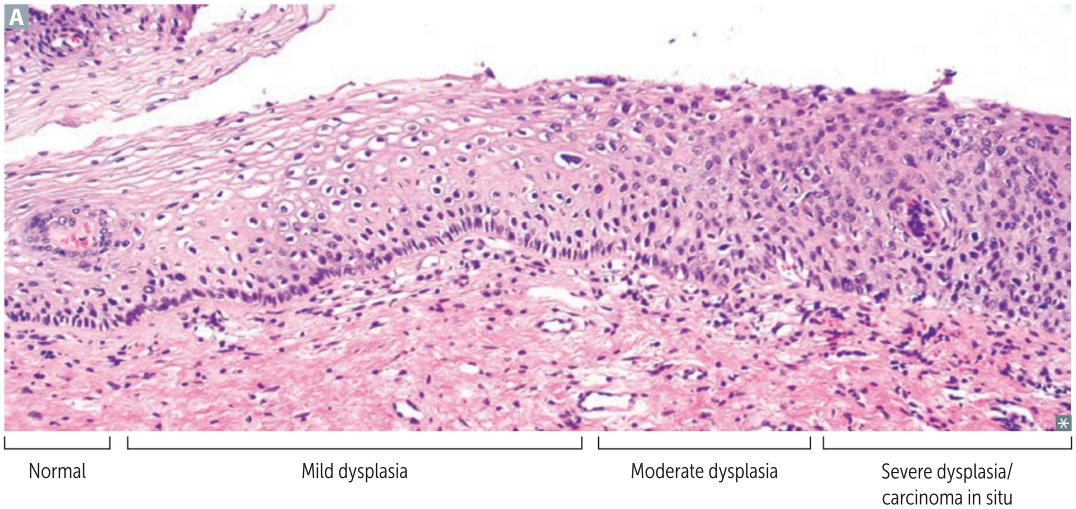
## ▶ PATHOLOGY—NEOPLASIA

**Neoplasia and neoplastic progression**

Uncontrolled, monoclonal proliferation of cells. Can be benign or malignant. Any neoplastic growth has two components: parenchyma (neoplastic cells) and supporting stroma (non-neoplastic; eg, blood vessels, connective tissue).




| | |
|---|---|
| **Normal cells** | ❶ Normal cells with basal → apical polarity. See cervical example A, which shows normal cells and spectrum of dysplasia, as discussed below. |
| **Dysplasia** | ❷ Loss of uniformity in cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, ↑ nuclear:cytoplasmic ratio) A; often reversible. |
| **Carcinoma in situ/ preinvasive** | ❸ Irreversible severe dysplasia that involves the entire thickness of epithelium but does not penetrate the intact basement membrane A. |
| **Invasive carcinoma** | ❹ Cells have invaded basement membrane using collagenases and hydrolases (metalloproteinases). Cell-cell contacts lost by inactivation of E-cadherin. |
| **Metastasis** | ❺ Spread to distant organ(s) via lymphatics or blood. |



**Tumor nomenclature**

**Carcinoma** implies epithelial origin, whereas **sarcoma** denotes mesenchymal origin. Both terms generally imply malignancy.

**Benign** tumors are usually well-differentiated and well-demarcated, with low mitotic activity, no metastases, and no necrosis.

**Malignant** tumors (cancers) may show poor differentiation, erratic growth, local invasion, metastasis, and ↓ apoptosis.

Terms for non-neoplastic malformations include hamartoma (disorganized overgrowth of tissues in their native location, eg, Peutz-Jeghers polyps) and choristoma (normal tissue in a foreign location, eg, gastric tissue located in distal ileum in Meckel diverticulum).

| CELL TYPE | BENIGN | MALIGNANT |
|---|---|---|
| **Epithelium** | Adenoma, papilloma | Adenocarcinoma, papillary carcinoma |
| **Mesenchyme** | | |
| Blood cells | | Leukemia, lymphoma |
| Blood vessels | Hemangioma | Angiosarcoma |
| Smooth muscle | Leiomyoma | Leiomyosarcoma |
| Striated muscle | Rhabdomyoma | Rhabdomyosarcoma |
| Connective tissue | Fibroma | Fibrosarcoma |
| Bone | Osteoma | Osteosarcoma |
| Fat | Lipoma | Liposarcoma |
| Melanocyte | Nevus/mole | Melanoma |

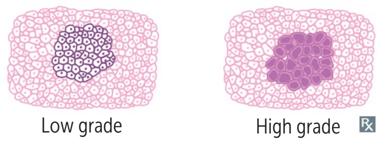
**Tumor grade vs stage**

Differentiation—degree to which a tumor resembles its tissue of origin. Well-differentiated tumors (often less aggressive) closely resemble their tissue of origin, whereas poorly differentiated tumors (often more aggressive) do not.

Anaplasia—complete lack of differentiation of cells in a malignant neoplasm.

**Grade**

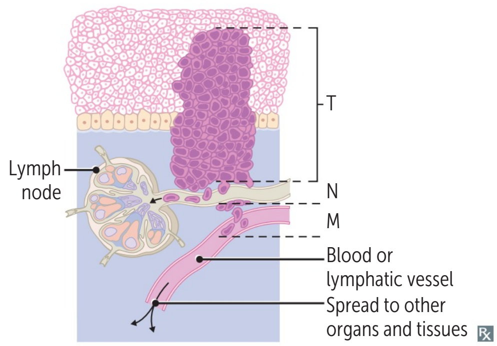
Degree of cellular differentiation and mitotic activity on histology. Ranges from low grade (well-differentiated) to high grade (poorly differentiated, undifferentiated, or anaplastic).




**Stage**

Degree of localization/spread based on site and size of 1° lesion, spread to regional lymph nodes, presence of metastases. Based on clinical (c) or pathologic (p) findings. Stage generally has more prognostic value than grade (eg, a high-stage yet low-grade tumor is usually worse than a low-stage yet high-grade tumor). **S**tage determines **S**urvival.

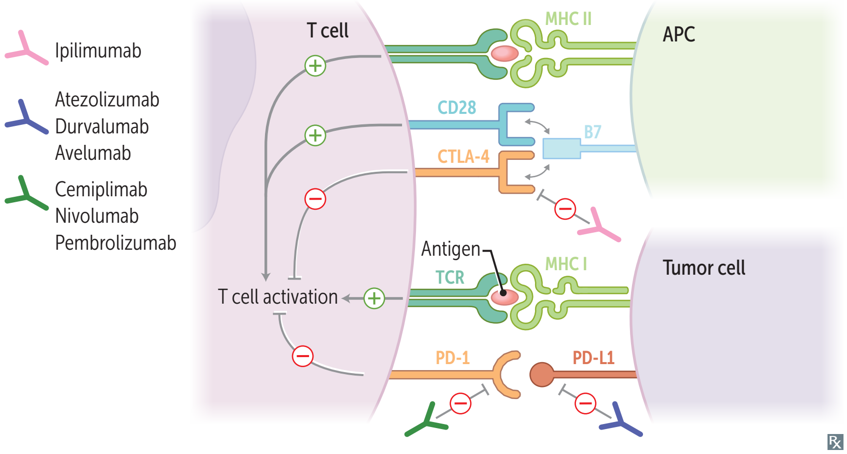
TNM staging system (**S**tage = **S**pread):
**T** = **T**umor size/invasiveness, **N** = **N**ode involvement, **M** = **M**etastases, eg, cT3N1M0. Each TNM factor has independent prognostic value; N and M are often most important.



**Hallmarks of cancer** Cancer is caused by (mostly acquired) DNA mutations that affect fundamental cellular processes (eg, growth, DNA repair, survival).

| HALLMARK | MECHANISM |
|---|---|
| **Growth signal self-sufficiency** | Mutations in genes encoding:<br>▪ Proto-oncogenes → ↑ growth factors → autocrine loop (eg, ↑ PDGF in brain tumors)<br>▪ Growth factor receptors → constitutive signaling (eg, *HER2/neu* in breast cancer)<br>▪ Signaling molecules (eg, *RAS*)<br>▪ Transcription factors (eg, *MYC*)<br>▪ Cell cycle regulators (eg, cyclins, CDKs) |
| **Anti-growth signal insensitivity** | ▪ Mutations in tumor suppressor genes (eg, *Rb*)<br>▪ Loss of E-cadherin function → loss of contact inhibition (eg, *NF2* mutations) |
| **Evasion of apoptosis** | Mutations in genes that regulate apoptosis (eg, *TP53*, *BCL2* → follicular B cell lymphoma). |
| **Limitless replicative potential** | Reactivation of telomerase → maintenance and lengthening of telomeres → prevention of chromosome shortening and cell aging. |
| **Sustained angiogenesis** | ↑ pro-angiogenic factors (eg, VEGF) or ↓ inhibitory factors. Factors may be produced by tumor or stromal cells. Vessels can sprout from existing capillaries (neoangiogenesis) or endothelial cells are recruited from bone marrow (vasculogenesis). Vessels may be leaky and/or dilated. |
| **Tissue invasion** | Loss of E-cadherin function → loosening of intercellular junctions → metalloproteinases degrade basement membrane and ECM → cells attach to ECM proteins (eg, laminin, fibronectin) → cells migrate through degraded ECM (“locomotion”) → vascular dissemination. |
| **Metastasis** | Tumor cells or emboli spread via lymphatics or blood → adhesion to endothelium → extravasation and homing. Site of metastasis can be predicted by site of 1° tumor, as the target organ is often the first-encountered capillary bed. Some cancers show organ tropism (eg, lung cancers commonly metastasize to adrenals). |
| **Warburg effect** | Shift of glucose metabolism away from mitochondrial oxidative phosphorylation toward glycolysis. Glycolysis provides rapidly dividing cancer cells with the carbon needed for synthesis of cellular structures. |
| **Immune evasion in cancer** | Normally, immune cells can recognize and attack tumor cells. For successful tumorigenesis, tumor cells must evade the immune system. Multiple escape mechanisms exist:<br>▪ ↓ MHC class I expression by tumor cells → cytotoxic T cells are unable to recognize tumor cells.<br>▪ Tumor cells secrete immunosuppressive factors (eg, TGF-β) and recruit regulatory T cells to down regulate immune response.<br>▪ Tumor cells up regulate immune checkpoint molecules, which inhibit immune response. |

| | |
|---|---|
| **Immune checkpoint interactions** | Signals that modulate T cell activation and function → ↓ immune response against tumor cells. Targeted by several cancer immunotherapies. Examples:<br>▪ Interaction between PD-1 (on T cells) and PD-L1/2 (on tumor cells or immune cells in tumor microenvironment) → T cell dysfunction (exhaustion). Inhibited by antibodies against PD-1 (eg, pembrolizumab, nivolumab, cemiplimab) or PD-L1 (eg, atezolizumab, durvalumab, avelumab).<br>▪ CTLA-4 on T cells outcompetes CD28 for B7 on APCs → loss of T cell costimulatory signal. Inhibited by ipilimumab (anti-CTLA-4 antibody). |



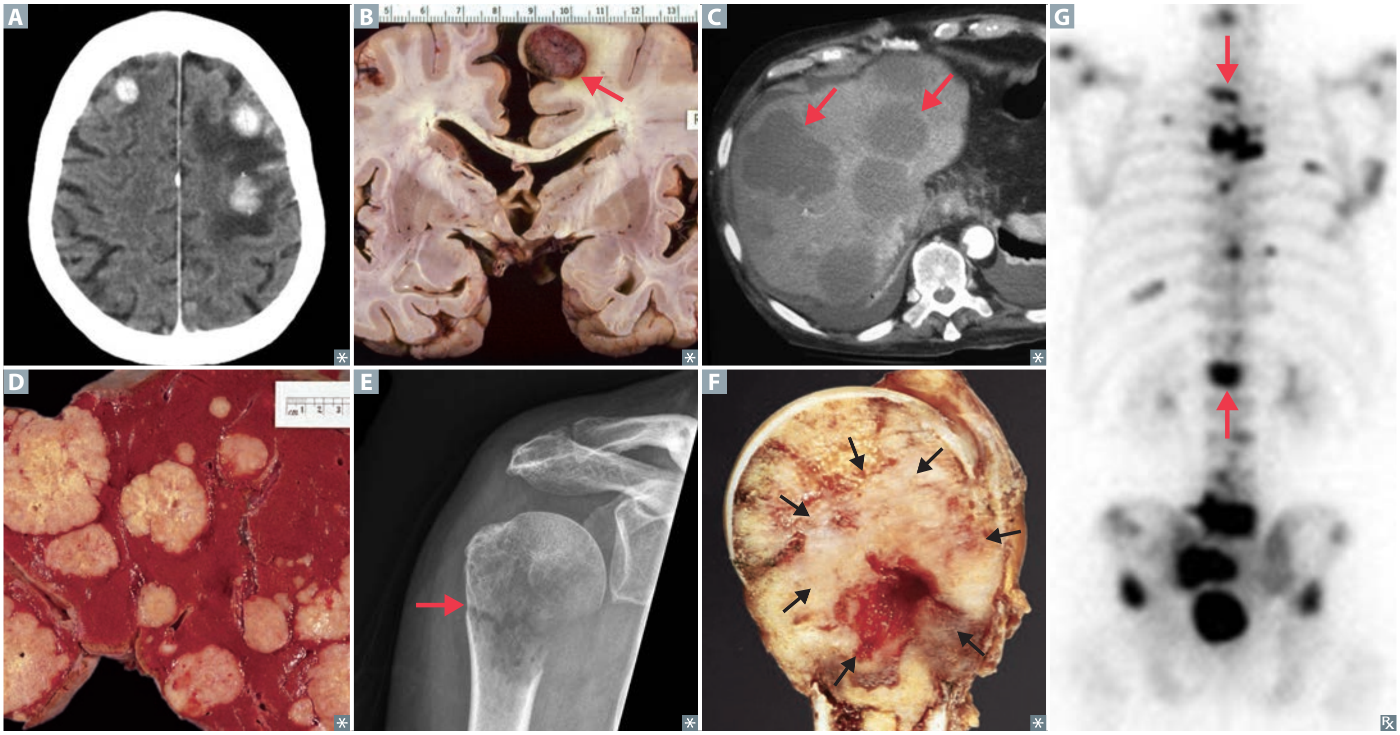

**Cancer epidemiology** Skin cancer (basal > squamous >> melanoma) is the most common cancer (not included below).

| | MALES | FEMALES | CHILDREN (AGE 0–14) | NOTES |
|---|---|---|---|---|
| **Cancer incidence** | 1. Prostate<br>2. Lung<br>3. Colon/rectum | 1. Breast<br>2. Lung<br>3. Colon/rectum | 1. Leukemia<br>2. CNS<br>3. Neuroblastoma | Lung cancer incidence has ↓ in males, but has not changed significantly in females. |
| **Cancer mortality** | 1. Lung<br>2. Prostate<br>3. Colon/rectum | 1. Lung<br>2. Breast<br>3. Colon/rectum | 1. Leukemia<br>2. CNS<br>3. Neuroblastoma | Cancer is the 2nd leading cause of death in the United States (heart disease is 1st). |

**Common metastases**

Most sarcomas spread hematogenously; most carcinomas spread via lymphatics. However, four carcinomas route hematogenously: follicular thyroid carcinoma, choriocarcinoma, renal cell carcinoma, and hepatocellular carcinoma.

| SITE OF METASTASIS | 1° TUMOR | NOTES |
|---|---|---|
| **Brain** | Lung > breast > melanoma, colon, kidney (lots of brain metastases can kill) | 50% of brain tumors are from metastases<br>Commonly seen as multiple well-circumscribed tumors at gray/white matter junction A B |
| **Liver** | Colon >> stomach > pancreas (cancer sometimes penetrates liver) | Liver C D and lung are the most common sites of metastasis after the regional lymph nodes |
| **Bone** | Prostate, breast > kidney, thyroid, lung (painful bones kill the lungs) | Bone metastasis E F >> 1° bone tumors (eg, multiple myeloma)<br>Predilection for axial skeleton G<br>Bone metastasis can be:<br>▪ Lytic (eg, thyroid, kidney, non-small cell lung cancer)<br>▪ Blastic (eg, prostate, small cell lung cancer)<br>▪ Mixed (eg, breast cancer) |



**Oncogenes**

Gain of function mutation converts proto-oncogene (normal gene) to oncogene → ↑ cancer risk. Requires damage to only one allele of a proto-oncogene.

| GENE | GENE PRODUCT | ASSOCIATED NEOPLASM |
|---|---|---|
| *ALK* | Receptor tyrosine kinase | Lung adenocarcinoma |
| *HER2/neu (ERBB2)* | Receptor tyrosine kinase | Breast and gastric carcinomas |
| *RET* | REceptor Tyrosine kinase | MEN 2A and 2B, medullary and papillary thyroid carcinoma, pheochromocytoma |
| *BCR-ABL* | Non-receptor tyrosine kinase | CML, ALL |
| *JAK2* | Non-receptor tyrosine kinase | Myeloproliferative neoplasms |
| *BRAF* | Serine/threonine kinase | Melanoma, non-Hodgkin lymphoma, colorectal carcinoma, papillary thyroid carcinoma, hairy cell leukemia |
| *c-KIT* | CytoKIne receptor | Gastrointestinal stromal tumor (GIST), mastocytosis |
| *c-MYC* | Transcription factor | Burkitt lymphoma |
| *MYCL1* | Transcription factor | Lung cancer |
| *MYCN (N-myc)* | Transcription factor | Neuroblastoma |
| *KRAS* | RAS GTPase | Colorectal, lung, pancreatic cancers |
| *BCL-2* | Antiapoptotic molecule (inhibits apoptosis) | Follicular and diffuse large B-Cell Lymphomas |

**Tumor suppressor genes**

Loss of function → ↑ cancer risk; both (two) alleles of a tumor suppressor gene must be lost for expression of disease (Knudson's 2-hit hypothesis).

| GENE | GENE PRODUCT | ASSOCIATED CONDITION |
|---|---|---|
| *APC* | Negative regulator of β-catenin/WNT pathway | Colorectal cancer (associated with FAP) |
| *BRCA1/BRCA2* | BRCA1/BRCA2 proteins | BReast, ovarian, prostate, pancreatic CAncers |
| *CDKN2A* | p16, blocks $G_1$ → S phase | Many cancers (eg, melanoma, lung) |
| *DCC* | DCC—Deleted in Colorecta Cancer | Colorectal cancer |
| *SMAD4 (DPC4)* | DPC—Deleted in Pancreatic Cancer | Pancreatic cancer, colorectal cancer |
| *MEN1* | MENin | Multiple Endocrine Neoplasia type 1 |
| *NF1* | Neurofibromin (Ras GTPase activating protein) | NeuroFibromatosis type 1 |
| *NF2* | Merlin (schwannomin) protein | NeuroFibromatosis type 2 |
| *PTEN* | Negative regulator of PI3k/AKT pathway | Prostate, breasT, and ENdometrial cancers |
| RB1 | Inhibits E2F; blocks $G_1$ → S phase | Retinoblastoma, osteosarcoma (bone cancer) |
| *TP53* | p53, activates p21, blocks $G_1$ → S phase | Most cancers, Li-Fraumeni syndrome (multiple malignancies at early age, aka, SBLA syndrome: Sarcoma, Breast, Leukemia, Adrenal gland) |
| *TSC1* | Hamartin protein | Tuberous sclerosis |
| *TSC2* | Tuberin ("2berin") | Tuberous sclerosis |
| *VHL* | Inhibits hypoxia-inducible factor 1a | von Hippel-Lindau disease |
| *WT1* | Urogenital development transcription factor | Wilms Tumor (nephroblastoma) |

### Carcinogens

| TOXIN | EXPOSURE | ORGAN | IMPACT |
|---|---|---|---|
| Aflatoxins (*Aspergillus*) | Stored grains and nuts | Liver | Hepatocellular carcinoma |
| Alkylating agents | Oncologic chemotherapy | Blood | Leukemia/lymphoma |
| Aromatic amines (eg, benzidine, 2-naphthylamine) | Textile industry (dyes), tobacco smoke (2-naphthylamine) | Bladder | Transitional cell carcinoma |
| Arsenic | Herbicides (vineyard workers), metal smelting, wood preservation | Liver<br>Lung<br>Skin | Hepatic angiosarcoma<br>Lung cancer<br>Squamous cell carcinoma |
| Asbestos | Old roofing material, shipyard workers | Lung | Bronchogenic carcinoma > mesothelioma |
| Tobacco smoke | | Bladder<br>Cervix<br>Esophagus<br><br>Kidney<br>Larynx<br>Lung<br><br>Oropharynx<br>Pancreas | Transitional cell carcinoma<br>Squamous cell carcinoma<br>Squamous cell carcinoma/adenocarcinoma<br>Renal cell carcinoma<br>Squamous cell carcinoma<br>Squamous cell and small cell carcinoma<br>Oropharyngeal cancer<br>Pancreatic adenocarcinoma |
| Ethanol | | Esophagus<br>Liver<br>Breast | Squamous cell carcinoma<br>Hepatocellular carcinoma<br>Breast cancer |
| Ionizing radiation | | Thyroid | Papillary thyroid carcinoma, leukemias |
| Nickel, chromium, beryllium, silica | Occupational exposure | Lung | Lung cancer |
| Nitrosamines | Smoked foods | Stomach | Gastric cancer (intestinal type) |
| Radon | Byproduct of uranium decay, accumulates in basements | Lung | Lung cancer (2nd leading cause after tobacco smoke) |
| Vinyl chloride | Used to make PVC pipes (plumbers) | LiVer | Hepatic angiosarcoma |

## Oncogenic microbes

| Microbe | Associated cancer |
|---|---|
| EBV | Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, 1° CNS lymphoma (in immunocompromised patients) |
| HBV, HCV | Hepatocellular carcinoma |
| HHV-8 | Kaposi sarcoma |
| HPV (usually types 16, 18) | Cervical and penile/anal carcinoma, head and neck cancer |
| *H pylori* | Gastric adenocarcinoma and MALT lymphoma |
| HTLV-1 | Adult T-cell Leukemia/Lymphoma |
| Liver fluke (*Clonorchis sinensis*) | Cholangiocarcinoma |
| *Schistosoma haematobium* | Squamous cell bladder cancer |

## Serum tumor markers

Tumor markers should not be used as the 1° tool for cancer diagnosis or screening. They may be used to monitor tumor recurrence and response to therapy, but definitive diagnosis is made via biopsy. Some can be associated with non-neoplastic conditions.

| MARKER | IMPORTANT ASSOCIATIONS | NOTES |
|---|---|---|
| **Alkaline phosphatase** | Metastases to bone or liver, Paget disease of bone, seminoma (placental ALP). | Exclude hepatic origin by checking LFTs and GGT levels. |
| **α-fetoprotein** | Hepatocellular carcinoma, endodermal sinus (yolk sac) tumor, mixed germ cell tumor, ataxia-telangiectasia, neural tube defects. | Normally made by fetus. Transiently elevated in pregnancy. High levels associated with neural tube and abdominal wall defects, low levels associated with Down syndrome. |
| **hCG** | Hydatidiform moles and Choriocarcinomas (Gestational trophoblastic disease), testicular cancer, mixed germ cell tumor. | Produced by syncytiotrophoblasts of the placenta. |
| **CA 15-3/CA 27-29** | Breast cancer. | |
| **CA 19-9** | Pancreatic adenocarcinoma. | |
| **CA 125** | Ovarian cancer. | |
| **Calcitonin** | Medullary thyroid carcinoma (alone and in MEN2A, MEN2B). | Calci2nin. |
| **CEA** | Colorectal and pancreatic cancers. Minor associations: gastric, breast, and medullary thyroid carcinomas. | CarcinoEmbryonic Antigen. Very nonspecific. |
| **Chromogranin** | Neuroendocrine tumors. | |
| **LDH** | Testicular germ cell tumors, ovarian dysgerminoma, other cancers. | Can be used as an indicator of tumor burden. |
| **Neuron-specific enolase** | Neuroendocrine tumors (eg, small cell lung cancer, carcinoid tumor, neuroblastoma). | |
| **PSA** | Prostate cancer. | Prostate-Specific Antigen. Also elevated in BPH and prostatitis. Questionable risk/benefit for screening. Marker for recurrence after treatment. |

**Important immunohistochemical stains**

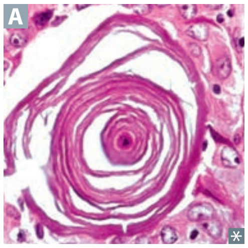
Determine primary site of origin for metastatic tumors and characterize tumors that are difficult to classify. Can have prognostic and predictive value.

| STAIN | TARGET | TUMORS IDENTIFIED |
|---|---|---|
| **Chromogranin and synaptophysin** | Neuroendocrine cells | Small cell carcinoma of the lung, carcinoid tumor, neuroblastoma |
| **Cytokeratin** | Epithelial cells | Epithelial tumors (eg, squamous cell carcinoma) |
| **Desmin** | Muscle | Muscle tumors (eg, rhabdomyosarcoma) |
| **GFAP** | NeuroGlia (eg, astrocytes, Schwann cells, oligodendrocytes) | Astrocytoma, Glioblastoma |
| **Neurofilament** | Neurons | Neuronal tumors (eg, neuroblastoma) |
| **PSA** | Prostatic epithelium | Prostate cancer |
| **S-100** | Neural crest cells | Melanoma, schwannoma, Langerhans cell histiocytosis |
| **TRAP** | Tartrate-resistant acid phosphatase | Hairy cell leukemia |
| **Vimentin** | Mesenchymal tissue (eg, fibroblasts, endothelial cells, macrophages) | Mesenchymal tumors (eg, sarcoma), but also many other tumors (eg, endometrial carcinoma, renal cell carcinoma, meningioma) |

**P-glycoprotein**

ATP-dependent efflux pump also known as multidrug resistance protein 1 (MDR1). Classically seen in adrenocortical carcinoma but also expressed by other cancer cells (eg, colon, liver). Used to pump out toxins, including chemotherapeutic agents (one mechanism of ↓ responsiveness or resistance to chemotherapy over time).

**Psammoma bodies**



Laminated, concentric spherules with dystrophic calcification A, PSAMMOMaS bodies are seen in:

- Papillary carcinoma of thyroid
- Somatostatinoma
- Adrenals (calcifying fibrous pseudotumor)
- Meningioma
- Malignant Mesothelioma
- Ovarian serous carcinoma
- Prolactinoma (Milk)
- Serous endometrial carcinoma

**Cachexia**

Weight loss, muscle atrophy, and fatigue that occur in chronic disease (eg, cancer, AIDS, heart failure, COPD). Mediated by TNF-α, IFN-γ, IL-1, and IL-6.

## Paraneoplastic syndromes

| MANIFESTATION | DESCRIPTION/MECHANISM | MOST COMMONLY ASSOCIATED TUMOR(S) |
|---|---|---|
| **Musculoskeletal and cutaneous** | | |
| **Dermatomyositis** | Progressive proximal muscle weakness, Gottron papules, heliotrope rash | Adenocarcinomas, especially ovarian |
| **Acanthosis nigricans** | Hyperpigmented velvety plaques in axilla and neck | Gastric adenocarcinoma and other visceral malignancies |
| **Sign of Leser-Trélat** | Sudden onset of multiple seborrheic keratoses | GI adenocarcinomas and other visceral malignancies |
| **Hypertrophic osteoarthropathy** | Abnormal proliferation of skin and bone at distal extremities → clubbing, arthralgia, joint effusions, periostosis of tubular bones | Adenocarcinoma of the lung |
| **Endocrine** | | |
| **Hypercalcemia** | PTHrP | $SCa^{2+}$mous cell carcinomas of lung, head, and neck; renal, bladder, breast, and ovarian carcinomas |
| | ↑ 1,25-$(OH)_2$ vitamin $D_3$ (calcitriol) | Lymphoma |
| **Cushing syndrome** | ↑ ACTH | Small cell lung cancer |
| **Hyponatremia (SIADH)** | ↑ ADH | Small cell lung cancer |
| **Hematologic** | | |
| **Polycythemia** | ↑ Erythropoietin<br>Paraneoplastic rise to High hematocrit levels | Pheochromocytoma, renal cell carcinoma, HCC, hemangioblastoma, leiomyoma |
| **Pure red cell aplasia** | Anemia with low reticulocytes | Thymoma |
| **Good syndrome** | Hypogammaglobulinemia | Thymoma |
| **Trousseau syndrome** | Migratory superficial thrombophlebitis | Adenocarcinomas, especially pancreatic |
| **Nonbacterial thrombotic (marantic) endocarditis** | Deposition of sterile platelet thrombi on heart valves | Adenocarcinomas, especially pancreatic |
| **Neuromuscular** | | |
| **Anti-NMDA receptor encephalitis** | Psychiatric disturbance, memory deficits, seizures, dyskinesias, autonomic instability, language dysfunction | Ovarian teratoma |
| **Opsoclonus-myoclonus ataxia syndrome** | "Dancing eyes, dancing feet" | Neuroblastoma (children), small cell lung cancer (adults) |
| **Paraneoplastic cerebellar degeneration** | Antibodies against antigens in Purkinje cells | Small cell lung cancer (anti-Hu), gynecologic and breast cancers (anti-Yo), and Hodgkin lymphoma (anti-Tr) |
| **Paraneoplastic encephalomyelitis** | Antibodies against Hu antigens in neurons | Small cell lung cancer |
| **Lambert-Eaton myasthenic syndrome** | Antibodies against presynaptic (P/Q-type) $Ca^{2+}$ channels at NMJ | Small cell lung cancer |
| **Myasthenia gravis** | Antibodies against postsynaptic ACh receptors at NMJ | Thymoma |

▶ NOTES

HIGH-YIELD PRINCIPLES IN

# Pharmacology

*"Cure sometimes, treat often, and comfort always."*

—Hippocrates

*"One pill makes you larger, and one pill makes you small."*

—Jefferson Airplane, *White Rabbit*

*"For the chemistry that works on one patient may not work for the next, because even medicine has its own conditions."*

—Suzy Kassem

*"I wondher why ye can always read a doctor's bill an' ye niver can read his purscription."*

—Finley Peter Dunne

*"Love is the drug I'm thinking of."*

—The Bryan Ferry Orchestra

Preparation for pharmacology questions is not as straightforward as in years past. The big change is that the USMLE Step 1 is moving away from pharmacotherapeutics. That means you will generally not be required to identify medications indicated for a specific condition. You still need to know all the mechanisms and important adverse effects of key drugs and their major variants. Obscure derivatives are low-yield. Learn their classic and distinguishing toxicities as well as major drug-drug interactions.

Reviewing associated biochemistry, physiology, and microbiology concepts can be useful while studying pharmacology. The exam has a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as on NSAIDs, which are covered throughout the text. Specific drug dosages or trade names are generally not testable. The exam may use graphs to test various pharmacology content, so make sure you are comfortable interpreting them.

## ▶ PHARMACOLOGY—PHARMACOKINETICS AND PHARMACODYNAMICS

### Enzyme kinetics

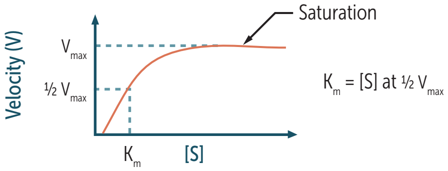
**Michaelis-Menten kinetics**

$K_m$ is inversely related to the affinity of the enzyme for its substrate.

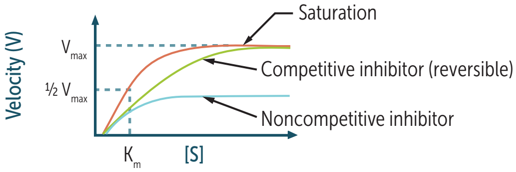
$V_{max}$ is directly proportional to the enzyme concentration.

Most enzymatic reactions follow a hyperbolic curve (ie, Michaelis-Menten kinetics); however, enzymatic reactions that exhibit a sigmoid curve usually indicate cooperative kinetics (eg, hemoglobin).

[S] = concentration of substrate; V = velocity.




Effects of enzyme inhibition




**Lineweaver-Burk plot**

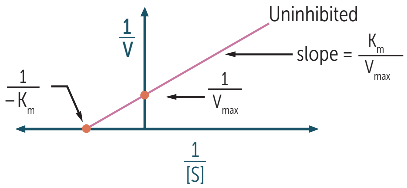
The closer to 0 on the Y-axis, the higher the $V_{max}$.

The closer to 0 on the X-axis, the higher the $K_m$.

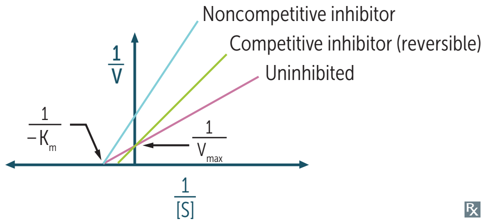
The higher the $K_m$, the lower the affinity.

**C**ompetitive inhibitors **c**ross each other, whereas **no**ncompetitive inhibitors do **not**.

**K**o**m**petitive **in**hibitors **in**crease **$K_m$**.




Effects of enzyme inhibition



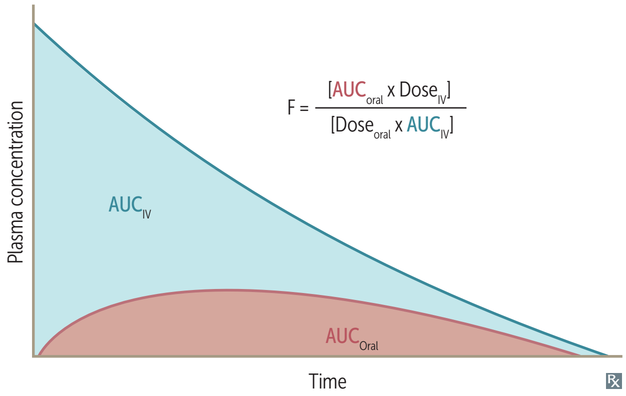

| | Competitive inhibitors, reversible | Competitive inhibitors, irreversible | Noncompetitive inhibitors |
|---|---|---|---|
| Resemble substrate | Yes | Yes | No |
| Overcome by ↑ [S] | Yes | No | No |
| Bind active site | Yes | Yes | No |
| Effect on $V_{max}$ | Unchanged | ↓ | ↓ |
| Effect on $K_m$ | ↑ | Unchanged | Unchanged |
| Pharmacodynamics | ↓ potency | ↓ efficacy | ↓ efficacy |

## Pharmacokinetics

### Bioavailability (F)

Fraction of administered drug reaching systemic circulation unchanged. For an IV dose, F = 100%.

Orally: F typically < 100% due to incomplete absorption and first-pass metabolism. Can be calculated from the area under the curve in a plot of plasma concentration over time.




### Volume of distribution ($V_d$)

Theoretical volume occupied by the total amount of drug in the body relative to its plasma concentration. Apparent $V_d$ of plasma protein–bound drugs can be altered by liver and kidney disease (↓ protein binding, ↑ $V_d$). Drugs may distribute in more than one compartment. Hemodialysis is most effective for drugs with a low $V_d$.

$$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$$

| $V_d$ | COMPARTMENT | DRUG TYPES |
|---|---|---|
| Low | Intravascular | Large/charged molecules; plasma protein bound |
| Medium | ECF | Small hydrophilic molecules |
| High | All tissues including fat | Small lipophilic molecules, especially if bound to tissue protein |

### Clearance (CL)

The volume of plasma cleared of drug per unit time. Clearance may be impaired with defects in cardiac, hepatic, or renal function.

$$CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e \text{ (elimination constant)}$$

### Half-life ($t_{1/2}$)

The time required to change the amount of drug in the body by ½ during elimination.

Steady state is a dynamic equilibrium in which drug concentration stays constant (ie, rate of drug elimination = rate of drug ingestion).

In first-order kinetics, a drug infused at a constant rate takes 4–5 half-lives to reach steady state. It takes 3.3 half-lives to reach 90% of the steady-state level.

$$t_{1/2} = \frac{0.7 \times V_d}{CL} \text{ in first-order elimination}$$

| # of half-lives | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| % remaining | 50% | 25% | 12.5% | 6.25% |

## Dosage calculations

$$\text{Loading dose} = \frac{C_p \times V_d}{F}$$

$$\text{Maintenance dose} = \frac{C_p \times CL \times \tau}{F}$$

$C_{ss}$ = target plasma concentration at steady state

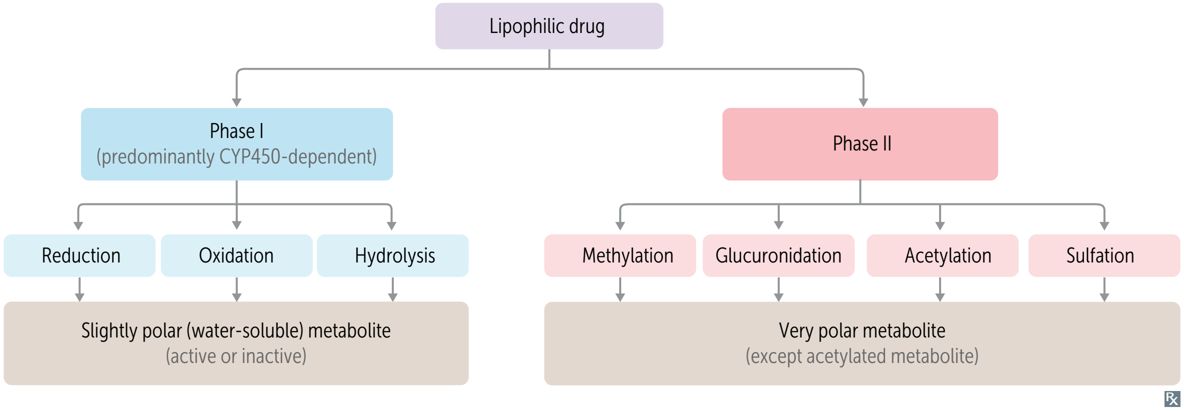
$\tau$ = dosage interval (time between doses), if not administered continuously

In renal or liver disease, maintenance dose ↓ and loading dose is usually unchanged.

Time to steady state depends primarily on $t_{1/2}$ and is independent of dose and dosing frequency.

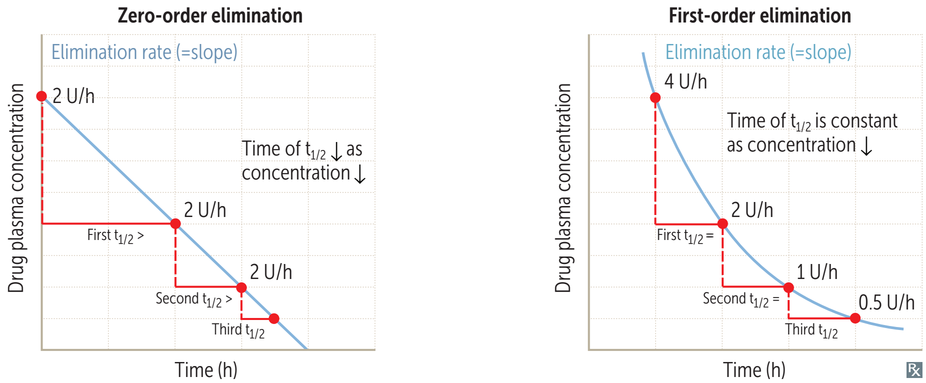
## Drug metabolism

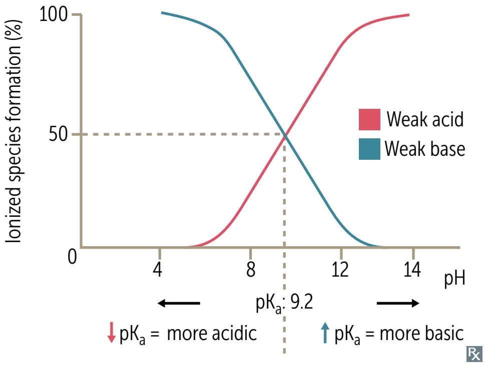
Geriatric patients lose phase I first. Patients who are slow acetylators have ↑ side effects from certain drugs because of ↓ rate of metabolism (eg, isoniazid).




## Elimination of drugs

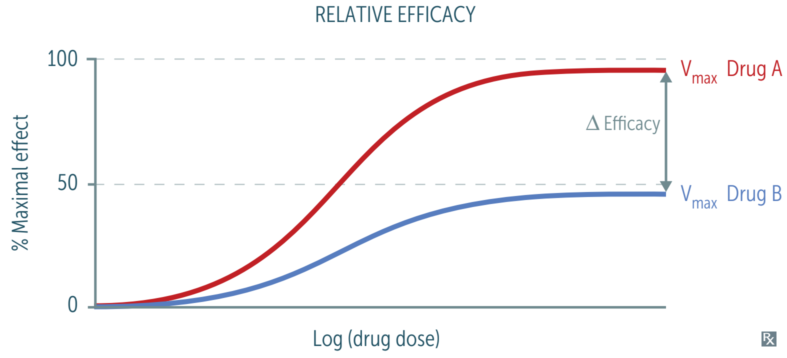
| | | |
|---|---|---|
| **Zero-order elimination** | Rate of elimination is constant regardless of $C_p$ (ie, constant **amount** of drug eliminated per unit time). $C_p$ ↓ linearly with time. Examples of drugs—**P**henytoin, **E**thanol, and **A**spirin (at high or toxic concentrations). | Capacity-limited elimination. **PEA** (a pea is round, shaped like the "**0**" in **zero**-order). |
| **First-order elimination** | Rate of **f**irst-order elimination is directly proportional to the drug concentration (ie, constant **fraction** of drug eliminated per unit time). $C_p$ ↓ exponentially with time. Applies to most drugs. | **F**low-dependent elimination. |



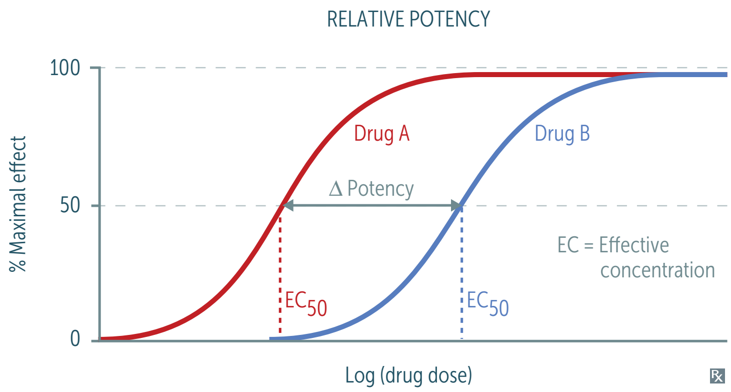
| | |
|---|---|
| **Urine pH and drug elimination** | Ionized species are trapped in urine and cleared quickly. Neutral forms can be reabsorbed. |
| **Weak acids** | Examples: phenobarbital, methotrexate, aspirin (salicylates). Trapped in basic environments. Treat overdose with sodium bicarbonate to alkalinize urine. $$\underset{\text{(lipid soluble)}}{RCOOH} \rightleftharpoons \underset{\text{(trapped)}}{RCOO^- + H^+}$$ |
| **Weak bases** | Examples: TCAs, amphetamines. Trapped in acidic environments. Treat overdose with ammonium chloride to acidify urine. $$\underset{\text{(trapped)}}{RNH_3^+} \rightleftharpoons \underset{\text{(lipid soluble)}}{RNH_2 + H^+}$$ TCA toxicity is generally treated with sodium bicarbonate to overcome the sodium channel-blocking activity of TCAs, but not for accelerating drug elimination. |
| **pKa** | pH at which drugs (weak acid or base) are 50% ionized and 50% nonionized. The pKa represents the strength of the weak acid or base.  |

## Efficacy vs potency

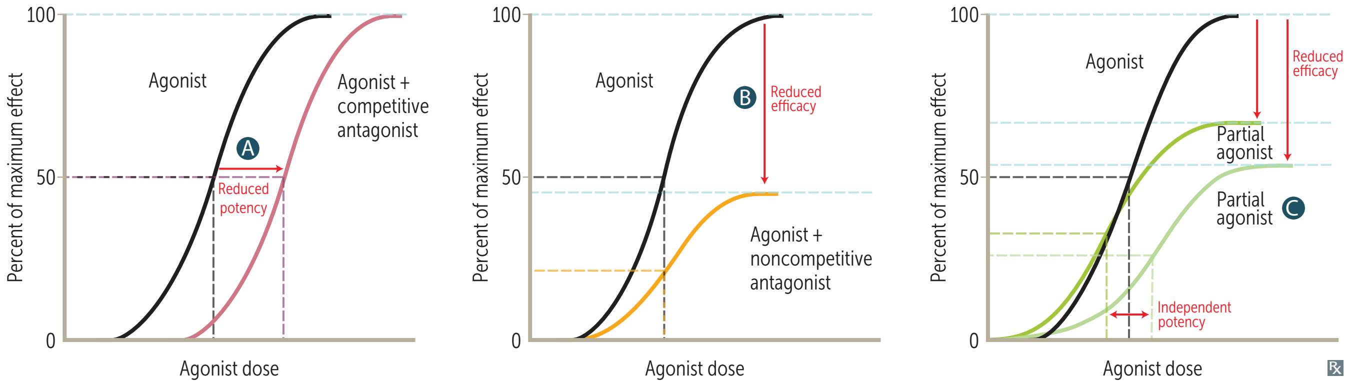
**Efficacy** Maximal effect a drug can produce. Represented by the y-value ($V_{max}$). ↑ y-value = ↑ $V_{max}$ = ↑ efficacy. Unrelated to potency (ie, efficacious drugs can have high or low potency). Partial agonists have less efficacy than full agonists.




**Potency** Amount of drug needed for a given effect. Represented by the x-value ($EC_{50}$). Left shifting = ↓ $EC_{50}$ = ↑ potency = ↓ drug needed. Unrelated to efficacy (ie, potent drugs can have high or low efficacy).



## Receptor binding




| AGONIST WITH | POTENCY | EFFICACY | REMARKS | EXAMPLE |
|---|---|---|---|---|
| **A** Competitive antagonist | ↓ | No change | **Can** be overcome by ↑ agonist concentration | Diazepam (agonist) + flumazenil (competitive antagonist) on $GABA_A$ receptor. |
| **B** Noncompetitive antagonist | No change | ↓ | **Cannot** be overcome by ↑ agonist concentration | Norepinephrine (agonist) + phenoxybenzamine (noncompetitive antagonist) on α-receptors. |
| **C** Partial agonist (alone) | Independent | ↓ | Acts at same site as full agonist | Morphine (full agonist) vs buprenorphine (partial agonist) at opioid μ-receptors. |

## Therapeutic index

Measurement of drug safety.

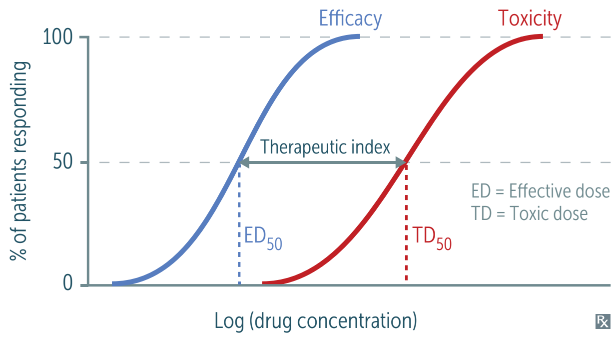
$$\frac{TD_{50}}{ED_{50}} = \frac{\text{median toxic dose}}{\text{median effective dose}}$$

Therapeutic window—range of drug concentrations that can safely and effectively treat disease.

**TITE**: **T**herapeutic **I**ndex = $TD_{50}$ / $ED_{50}$.

Safer drugs have higher TI values. Drugs with lower TI values frequently require monitoring (eg, **w**arfarin, **t**heophylline, **d**igoxin, **a**ntiepileptic drugs, **l**ithium; **W**arning! **T**hese **d**rugs **a**re **l**ethal!).

$LD_{50}$ (lethal median dose) often replaces $TD_{50}$ in animal studies.

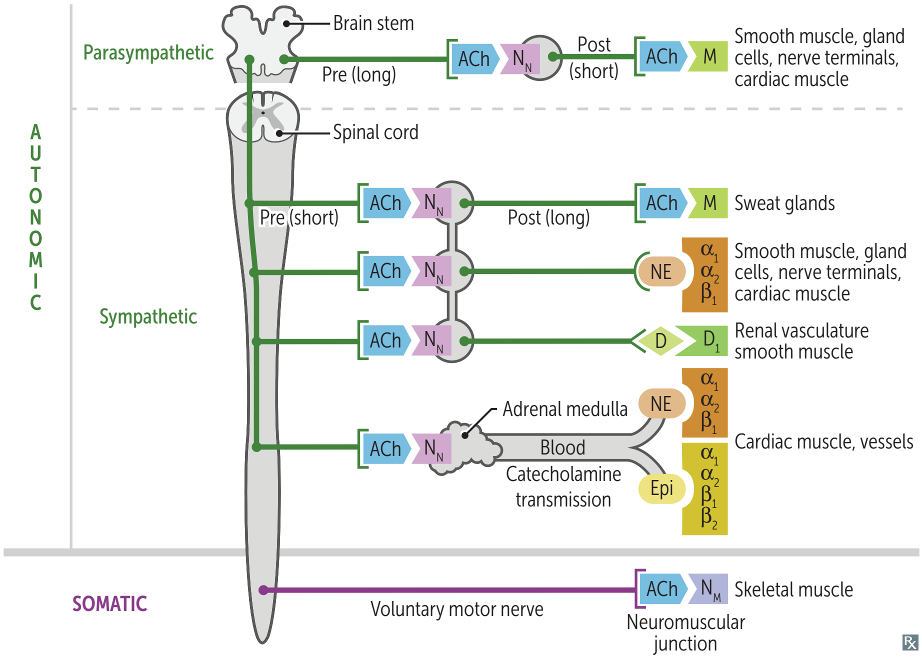


## Drug effect modifications

| TERM | DEFINITION | EXAMPLE |
|---|---|---|
| **Additive** | Effect of substances A and B together is equal to the sum of their individual effects | Aspirin and acetaminophen<br>"2 + 2 = 4" |
| **Permissive** | Presence of substance A is required for the full effects of substance B | Cortisol on catecholamine responsiveness |
| **Synergistic** | Effect of substances A and B together is greater than the sum of their individual effects | Clopidogrel with aspirin<br>"2 + 2 > 4" |
| **Potentiation** | Similar to synergism, but drug B with no therapeutic action enhances the therapeutic action of drug A | Carbidopa only blocks enzyme to prevent peripheral conversion of levodopa<br>"2 + 0 > 2" |
| **Antagonistic** | Effect of substances A and B together is less than the sum of their individual effects | Ethanol antidote for methanol toxicity<br>"2 + 2 < 4" |
| **Tachyphylactic** | Acute decrease in response to a drug after initial/repeated administration | Hydralazine, nitrates, niacin, phenylephrine, LSD, MDMA |

## ▶ PHARMACOLOGY—AUTONOMIC DRUGS

### Autonomic receptors




Pelvic splanchnic nerves and CNs III, VII, IX and X are part of the parasympathetic nervous system.
Adrenal medulla is directly innervated by preganglionic sympathetic fibers.
Sweat glands are part of the sympathetic pathway but are innervated by cholinergic fibers (sympathetic nervous system results in a "chold" sweat).

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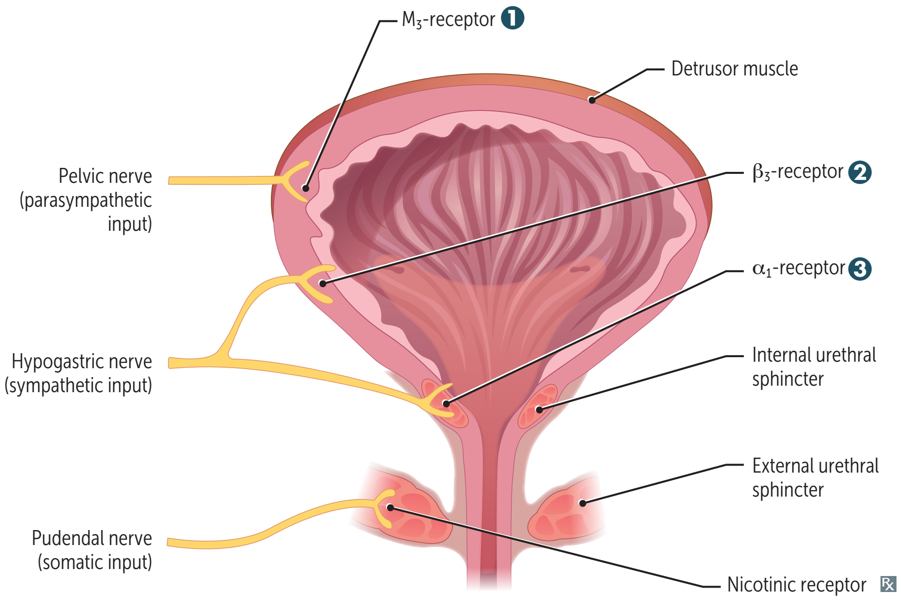
**Acetylcholine receptors**

Nicotinic ACh receptors are ligand-gated channels allowing efflux of $K^+$ and influx of $Na^+$ and in some cases $Ca^{2+}$. Two subtypes: $N_N$ (found in autonomic ganglia, adrenal medulla) and $N_M$ (found in neuromuscular junction of skeletal muscle).
Muscarinic ACh receptors are G-protein–coupled receptors that usually act through 2nd messengers. 5 subtypes: $M_{1-5}$ found in heart, smooth muscle, brain, exocrine glands, and on sweat glands (cholinergic sympathetic).

## Micturition control

Micturition center in pons regulates involuntary bladder function via coordination of sympathetic and parasympathetic nervous systems.

- ⊕ sympathetic → ↑ urinary retention.
- ⊕ parasympathetic → ↑ urine voiding. Some autonomic drugs act on smooth muscle receptors to treat bladder dysfunction.



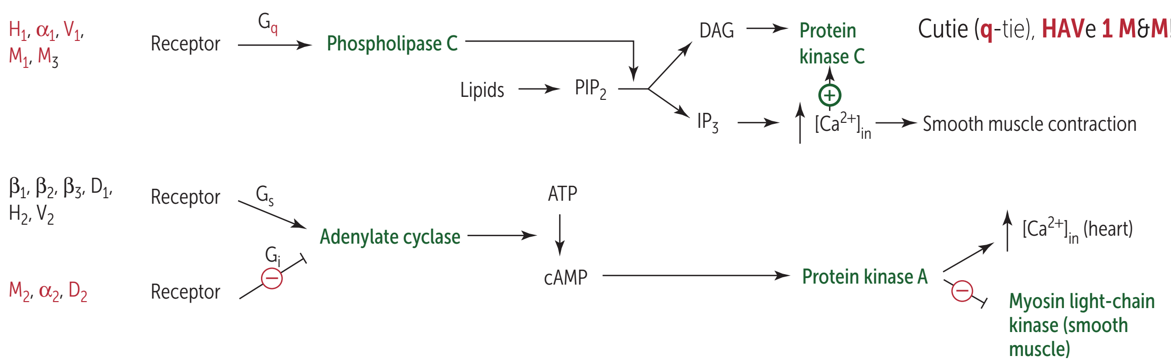

| DRUGS | MECHANISM | APPLICATIONS |
|---|---|---|
| ❶ **Muscarinic antagonists** (eg, oxybutynin) | ⊖ M$_3$ receptor → relaxation of detrusor smooth muscle → ↓ detrusor overactivity | Urgency incontinence |
| ❶ **Muscarinic agonists** (eg, bethanechol) | ⊕ M$_3$ receptor → contraction of detrusor smooth muscle → ↑ bladder emptying | Urinary retention |
| ❷ **Sympathomimetics** (eg, mirabegron) | ⊕ β$_3$ receptor → relaxation of detrusor smooth muscle → ↑ bladder capacity | Urgency incontinence |
| ❸ **α$_1$-blockers** (eg, tamsulosin) | ⊖ α$_1$-receptor → relaxation of smooth muscle (bladder neck, prostate) → ↓ urinary obstruction | BPH |

## Tissue distribution of adrenergic receptors

| | α$_1$ receptors | α$_2$ receptors | β$_1$ receptors | β$_2$ receptors | β$_3$ receptors |
|---|---|---|---|---|---|
| Cardiac muscle | – | – | +++ | + | + |
| Skeletal muscle | – | – | – | ++ | – |
| Vascular smooth muscle | +++ | + | – | ++ | + |
| Bronchial smooth muscle | – | – | – | ++ | – |
| Liver | + | – | – | +++ | – |
| Adipose tissue | + | + | + | – | ++ |
| CNS | ++ | ++ | ++ | ++ | – |
| Bladder neck/prostate | +++ | + | – | – | +++ |

### G-protein–linked second messengers

| RECEPTOR | G-PROTEIN CLASS | MAJOR FUNCTIONS |
|---|---|---|
| **Adrenergic** | | |
| $\alpha_1$ | q | ↑ vascular smooth muscle contraction, ↑ pupillary dilator muscle contraction (mydriasis), ↑ intestinal and bladder sphincter muscle contraction |
| $\alpha_2$ | i | ↓ sympathetic (adrenergic) outflow, ↓ insulin release, ↓ lipolysis, ↑ platelet aggregation, ↓ aqueous humor production |
| $\beta_1$ | s | ↑ heart rate, ↑ contractility (**one** heart), ↑ renin release, ↑ lipolysis |
| $\beta_2$ | s | Vasodilation, bronchodilation (**two** lungs), ↑ lipolysis, ↑ insulin release, ↑ glycogenolysis, ↓ uterine tone (tocolysis), ↑ aqueous humor production, ↑ cellular $K^+$ uptake |
| $\beta_3$ | s | ↑ lipolysis, ↑ thermogenesis in skeletal muscle, ↑ bladder relaxation |
| **Cholinergic** | | |
| $M_1$ | q | Mediates higher cognitive functions, stimulates enteric nervous system |
| $M_2$ | i | ↓ heart rate and contractility of atria |
| $M_3$ | q | ↑ exocrine gland secretions (eg, lacrimal, sweat, salivary, gastric acid), ↑ gut peristalsis, ↑ bladder contraction, bronchoconstriction, ↑ pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation), ↑ insulin release, endothelium-mediated vasodilation |
| **Dopamine** | | |
| $D_1$ | s | Relaxes renal vascular smooth muscle, activates direct pathway of striatum |
| $D_2$ | i | Modulates transmitter release, especially in brain, inhibits indirect pathway of striatum |
| **Histamine** | | |
| $H_1$ | q | ↑ nasal and bronchial mucus production, ↑ vascular permeability, bronchoconstriction, pruritus, pain |
| $H_2$ | s | ↑ gastric acid secretion |
| **Vasopressin** | | |
| $V_1$ | q | ↑ vascular smooth muscle contraction |
| $V_2$ | s | ↑ $H_2O$ permeability and reabsorption via upregulating aquaporin-**2** in collecting **two**bules (tubules) of kidney, ↑ release of vWF |



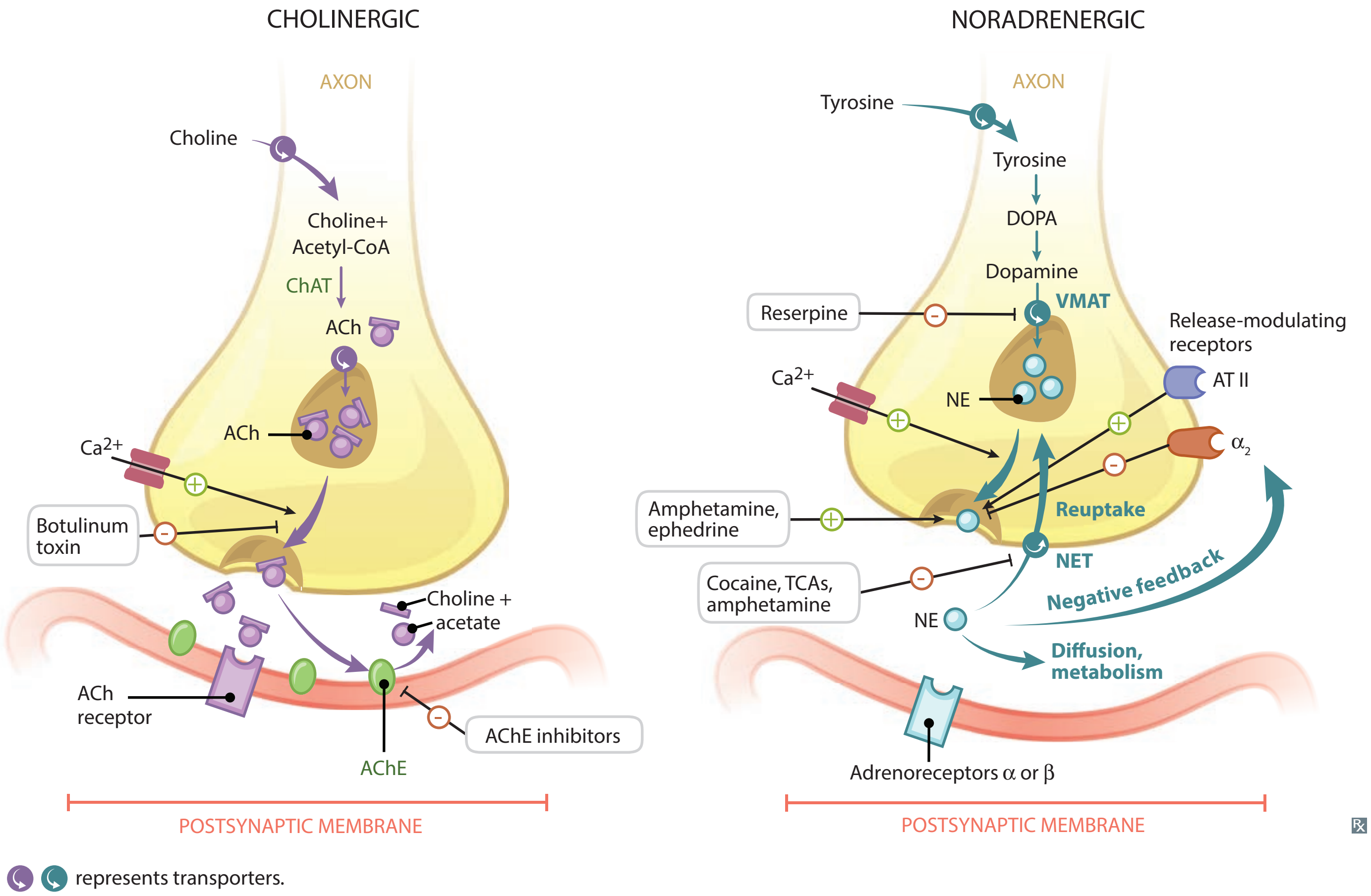

Cutie (**q**-tie), **HAVe 1 M&M**!

People who are **too (2) MAD** inhibit themselves.

## Autonomic drugs

Release of norepinephrine from a sympathetic nerve ending is modulated by NE itself, acting on presynaptic $\alpha_2$-autoreceptors → negative feedback.

Amphetamines use the NE transporter (NET) to enter the presynaptic terminal, where they utilize the vesicular monoamine transporter (VMAT) to enter neurosecretory vesicles. This displaces NE from the vesicles. Once NE reaches a concentration threshold within the presynaptic terminal, the action of NET is reversed, and NE is expelled into the synaptic cleft, contributing to the characteristics and effects of ↑ NE observed in patients taking amphetamines.



**Cholinomimetic agents** Watch for exacerbation of COPD, asthma, and peptic ulcers in susceptible patients.

| DRUG | ACTION | APPLICATIONS |
|---|---|---|
| **Direct agonists** | | |
| **Bethanechol** | Activates bladder smooth muscle; resistant to AChE. No nicotinic activity. "Bethany, call me to activate your bladder." | Urinary retention. |
| **Carbachol** | Carbon copy of acetylcholine (but resistant to AChE). | Constricts pupil and relieves intraocular pressure in open-angle glaucoma. |
| **Methacholine** | Stimulates muscarinic receptors in airway when inhaled. | Challenge test for diagnosis of asthma. |
| **Pilocarpine** | Contracts ciliary muscle of eye (open-angle glaucoma), pupillary sphincter (closed-angle glaucoma); resistant to AChE, can cross blood-brain barrier (tertiary amine). "You cry, drool, and sweat on your 'pilow.'" | Potent stimulator of sweat, tears, and saliva<br>Open-angle and closed-angle glaucoma, xerostomia (Sjögren syndrome). |
| **Indirect agonists (anticholinesterases)** | | |
| **Donepezil, rivastigmine, galantamine** | ↑ ACh. | 1st line for Alzheimer disease (Dona Riva forgot to dance at the gala). |
| **Edrophonium** | ↑ ACh. | Historically used to diagnose myasthenia gravis; replaced by anti-AChR Ab (anti-acetylcholine receptor antibody) test. |
| **Neostigmine** | ↑ ACh.<br>Neo CNS = no CNS penetration due to positive charge (quaternary amine). | Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative). |
| **Pyridostigmine** | ↑ ACh; ↑ muscle strength. Used with glycopyrrolate, hyoscyamine, or propantheline to control pyridostigmine side effects.<br>Pyridostigmine gets rid of myasthenia gravis. | Myasthenia gravis (long acting); does not penetrate CNS (quaternary amine). |
| **Physostigmine** | ↑ ACh. Phreely (freely) crosses blood-brain barrier as not charged → CNS (tertiary amine). | Antidote for anticholinergic toxicity; physostigmine "phyxes" atropine overdose. |

**Anticholinesterase poisoning** Often due to organophosphates (eg, parathion) that irreversibly inhibit AChE. Organophosphates commonly used as insecticides; poisoning usually seen in farmers.

| | | |
|---|---|---|
| **Muscarinic effects** | Diarrhea, Urination, Miosis, Bronchospasm, Bradycardia, Emesis, Lacrimation, Sweating, Salivation. | DUMBBELSS.<br>Reversed by atropine, a competitive inhibitor.<br>Atropine can cross BBB to relieve CNS symptoms. |
| **Nicotinic effects** | Neuromuscular blockade (mechanism similar to succinylcholine). | Reversed by pralidoxime, regenerates AChE via dephosphorylation if given early.<br>Pralidoxime (quaternary amine) does not readily cross BBB. |
| **CNS effects** | Respiratory depression, lethargy, seizures, coma. | |

## Muscarinic antagonists

| DRUGS | ORGAN SYSTEMS | APPLICATIONS |
|---|---|---|
| **Atropine, homatropine, tropicamide** | Eye | Produce mydriasis and cycloplegia |
| **Benztropine, trihexyphenidyl** | CNS | Parkinson disease ("park my Benz")<br>Acute dystonia |
| **Glycopyrrolate** | GI, respiratory | Parenteral: preoperative use to reduce airway secretions<br>Oral: reduces drooling, peptic ulcer |
| **Hyoscyamine, dicyclomine** | GI | Antispasmodics for irritable bowel syndrome |
| **Ipratropium, tiotropium** | Respiratory | COPD, asthma<br>Duration: tiotropium > ipratropium |
| **Solifenacin, Oxybutynin, Flavoxate, Tolterodine** | Genitourinary | Reduce bladder spasms and urge urinary incontinence (overactive bladder)<br>Make bladder **SOFT** |
| **Scopolamine** | CNS | Motion sickness |

**Atropine** Muscarinic antagonist. Used to treat bradycardia and for ophthalmic applications.

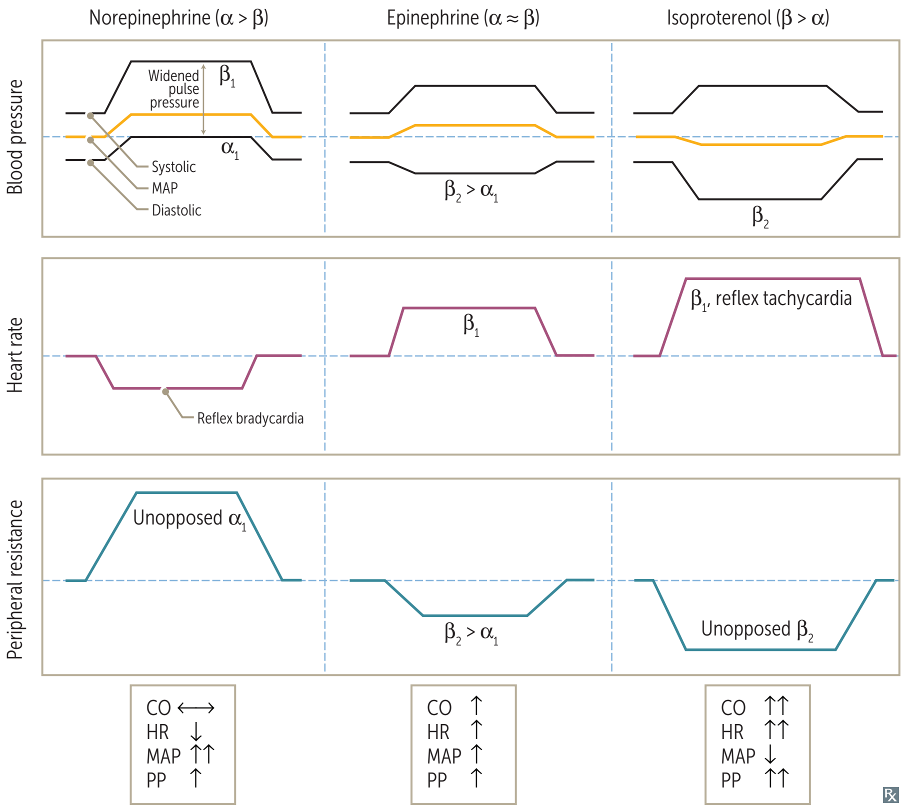
| ORGAN SYSTEM | ACTION | NOTES |
|---|---|---|
| Eye | ↑ pupil dilation, cycloplegia | Blocks muscarinic effects (**DUMBBELSS**) of anticholinesterases, but not the nicotinic effects |
| Airway | Bronchodilation, ↓ secretions | |
| Stomach | ↓ acid secretion | |
| Gut | ↓ motility | |
| Bladder | ↓ urgency in cystitis | |
| ADVERSE EFFECTS | ↑ body **temperature** (due to ↓ sweating); ↑ **HR**; dry mouth; **dry, flushed skin**; **cycloplegia**; constipation; **disorientation**<br>Can cause acute angle-closure glaucoma in elderly (due to mydriasis), **urinary retention** in men with prostatic hyperplasia, and hyperthermia in infants | Side effects:<br>**Hot** as a hare<br>**Fast** as a fiddle<br>**Dry** as a bone<br>**Red** as a beet<br>**Blind** as a bat<br>**Mad** as a hatter<br>**Full** as a flask<br>Jimson weed (*Datura*) → gardener's pupil (mydriasis due to plant alkaloids) |

### Sympathomimetics

| DRUG | ACTION | HEMODYNAMIC CHANGES | APPLICATIONS |
|---|---|---|---|
| **Direct sympathomimetics** | | | |
| **Albuterol, salmeterol, terbutaline** | $\beta_2 > \beta_1$ | ↑ HR (little effect) | **A**lbuterol for **a**cute asthma/COPD. **S**almeterol for **s**erial (long-term) asthma/COPD. Terbutaline for acute bronchospasm in asthma and tocolysis. |
| **Dobutamine** | $\beta_1 > \beta_2, \alpha$ | —/↓ BP, ↑ HR, ↑ CO | Cardiac stress testing, acute decompensated heart failure (HF) with cardiogenic shock (inotrope) |
| **Dopamine** | $D_1 = D_2 > \beta > \alpha$ | ↑ BP (high dose), ↑ HR, ↑ CO | Unstable bradycardia, shock; inotropic and chronotropic effects at lower doses via β effects; vasoconstriction at high doses via α effects. |
| **Epinephrine** | $\beta > \alpha$ | ↑ BP (high dose), ↑ HR, ↑ CO | Anaphylaxis, asthma, shock, open-angle glaucoma; α effects predominate at high doses. Stronger effect at $\beta_2$-receptor than norepinephrine. |
| **Fenoldopam** | $D_1$ | ↓ BP (vasodilation), ↑ HR, ↑ CO | Postoperative hypertension, hypertensive crisis. Vasodilator (coronary, peripheral, renal, and splanchnic). Promotes natriuresis. Can cause hypotension, tachycardia, flushing, headache. |
| **Isoproterenol** | $\beta_1 = \beta_2$ | ↓ BP (vasodilation), ↑ HR, ↑ CO | Electrophysiologic evaluation of tachyarrhythmias. Can worsen ischemia. Has negligible α effect. |
| **Midodrine** | $\alpha_1$ | ↑ BP (vasoconstriction), ↓ HR, ↔/↓ CO | Autonomic insufficiency and postural hypotension. May exacerbate supine hypertension. |
| **Mirabegron** | $\beta_3$ | | Urinary urgency or incontinence or overactive bladder. Think "mira**b3**gron." |
| **Norepinephrine** | $\alpha_1 > \alpha_2 > \beta_1$ | ↑ BP, ↓ HR (reflex bradycardia from ↑ BP due to $\alpha_1$ agonism outweighs direct $\beta_1$ chronotropic effect), —/↑ CO | Hypotension, septic shock. |
| **Phenylephrine** | $\alpha_1 > \alpha_2$ | ↑ BP (vasoconstriction), ↓ HR, —/↓ CO | Hypotension (vasoconstrictor), ocular procedures (mydriatic), rhinitis (decongestant), ischemic priapism. |
| **Indirect sympathomimetics** | | | |
| **Amphetamine** | Indirect general agonist, reuptake inhibitor, also releases stored catecholamines. | | Narcolepsy, obesity, ADHD. |
| **Cocaine** | Indirect general agonist, reuptake inhibitor. Causes vasoconstriction and local anesthesia. Caution when giving β-blockers if cocaine intoxication is suspected (unopposed $\alpha_1$ activation → ↑↑↑ BP, coronary vasospasm). | | Causes mydriasis in eyes with intact sympathetic innervation → used to confirm Horner syndrome. |
| **Ephedrine** | Indirect general agonist, releases stored catecholamines. | | Nasal decongestion (pseudoephedrine), urinary incontinence, hypotension. |

**Physiologic effects of sympathomimetics**

NE ↑ systolic and diastolic pressures as a result of $\alpha_1$-mediated vasoconstriction → ↑ mean arterial pressure → reflex bradycardia. However, isoproterenol (rarely used) has little α effect but causes $\beta_2$-mediated vasodilation, resulting in ↓ mean arterial pressure and ↑ heart rate through $\beta_1$ and reflex activity.

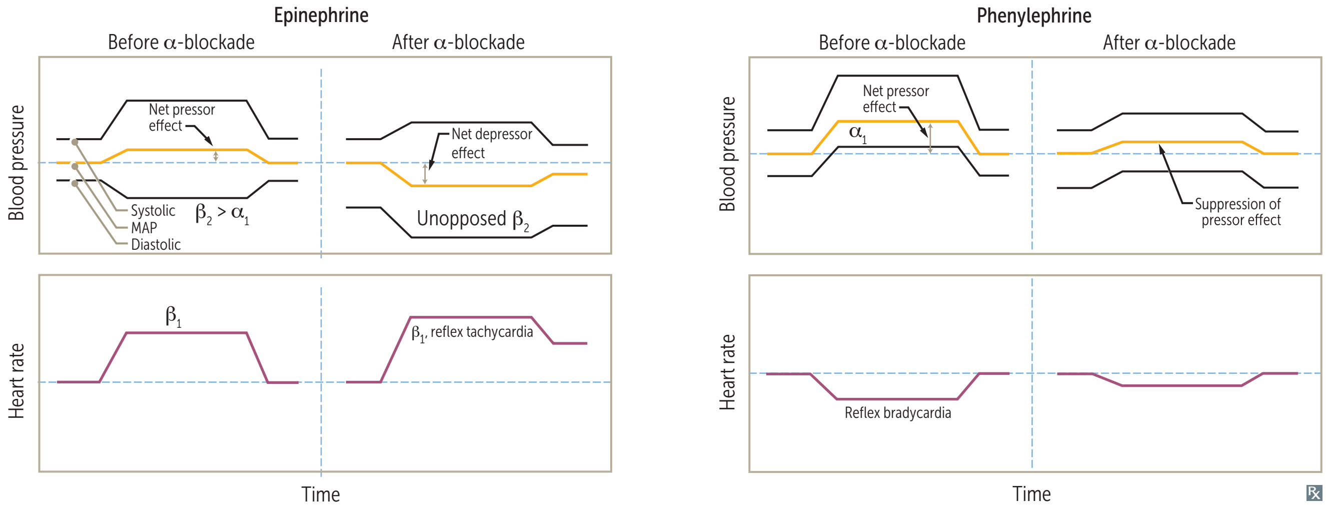



## Sympatholytics ($\alpha_2$-agonists)

| DRUG | APPLICATIONS | ADVERSE EFFECTS |
|---|---|---|
| **Clonidine, guanfacine** | Hypertensive urgency (limited situations), ADHD, Tourette syndrome, symptom control in opioid withdrawal | CNS depression, bradycardia, hypotension, respiratory depression, miosis, rebound hypertension with abrupt cessation |
| **α-methyldopa** | Hypertension in pregnancy | Direct Coombs ⊕ hemolysis, drug-induced lupus, hyperprolactinemia |
| **Tizanidine** | Relief of spasticity | Hypotension, weakness, xerostomia |

## α-blockers

| DRUG | APPLICATIONS | ADVERSE EFFECTS |
|---|---|---|
| **Nonselective** | | |
| **Phenoxybenzamine** | Irreversible. Pheochromocytoma (used preoperatively) to prevent catecholamine (hypertensive) crisis. | Orthostatic hypotension, reflex tachycardia. |
| **Phentolamine** | Reversible. Given to patients on MAO inhibitors who eat tyramine-containing foods and for severe cocaine-induced hypertension (2nd line). Also used to treat norepinephrine extravasation. | |
| **$\alpha_1$ selective (-osin ending)** | | |
| **Prazosin, terazosin, doxazosin, tamsulosin** | Urinary symptoms of BPH; PTSD (prazosin); hypertension (except tamsulosin). | 1st-dose orthostatic hypotension, dizziness, headache. |
| **$\alpha_2$ selective** | | |
| **Mirtazapine** | Depression. | Sedation, ↑ serum cholesterol, ↑ appetite. |




Epinephrine response exhibits reversal of mean arterial pressure from a net increase (the α response) to a net decrease (the $\beta_2$ response).

Phenylephrine response is suppressed but not reversed because it is a "pure" α-agonist (lacks β-agonist properties).

**β-blockers** Acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol.

| APPLICATION | ACTIONS | NOTES/EXAMPLES |
|---|---|---|
| Angina pectoris | ↓ heart rate and contractility → ↓ $O_2$ consumption | |
| Glaucoma | ↓ production of aqueous humor | Timolol |
| Heart failure | Blockade of neurohormonal stress → prevention of deleterious cardiac remodeling → ↓ mortality | **B**isoprolol, **c**arvedilol, **m**etoprolol (β-blockers **c**urb **m**ortality) |
| Hypertension | ↓ cardiac output, ↓ renin secretion (due to $\beta_1$-receptor blockade on JG cells) | |
| Hyperthyroidism/thyroid storm | Symptom control (↓ heart rate, ↓ tremor) | Propranolol |
| Hypertrophic cardiomyopathy | ↓ heart rate → ↑ filling time, relieving obstruction | |
| Myocardial infarction | ↓ $O_2$ demand (short-term), ↓ mortality (long-term) | |
| Supraventricular tachycardia | ↓ AV conduction velocity (class II antiarrhythmic) | Metoprolol, esmolol |
| Variceal bleeding | ↓ hepatic venous pressure gradient and portal hypertension (prophylactic use) | Nadolol, propranolol, carvedilol |
| ADVERSE EFFECTS | Erectile dysfunction, cardiovascular (bradycardia, AV block, HF), CNS (seizures, sleep alterations), dyslipidemia (metoprolol), masked hypoglycemia, asthma/COPD exacerbations | Use of β-blockers for acute cocaine-associated chest pain remains controversial due to unsubstantiated concern for unopposed α-adrenergic stimulation |
| SELECTIVITY | $\beta_1$-selective antagonists ($\beta_1 > \beta_2$)—**a**cebutolol (partial agonist), **a**tenolol, **b**etaxolol, **b**isoprolol, **e**smolol, **m**etoprolol | Selective antagonists mostly go from **A** to **M** ($\beta_1$ with **1**st half of alphabet) |
| | Nonselective antagonists ($\beta_1 = \beta_2$)—**n**adolol, **p**indolol (partial agonist), **p**ropranolol, **t**imolol | **N**on**Z**elective antagonists mostly go from **N** to **Z** ($\beta_2$ with **2**nd half of alphabet) |
| | Nonselective α- and β-antagonists—carved**ilol**, labet**alol** | Nonselective α- and β-antagonists have **modified suffixes** (instead of "-olol") |
| | Nebivolol combines cardiac-selective $\beta_1$-adrenergic blockade with stimulation of $\beta_3$-receptors (activate NO synthase in the vasculature and ↓ SVR) | **N**ebiv**O**lol increases **NO** |

**Phosphodiesterase inhibitors**

Phosphodiesterase (PDE) inhibitors inhibit PDE, which catalyzes the hydrolysis of cAMP and/or cGMP, and thereby increase cAMP and/or cGMP. These inhibitors have varying specificity for PDE isoforms and thus have different clinical uses.

| TYPE OF INHIBITOR | MECHANISM OF ACTION | CLINICAL USES | ADVERSE EFFECTS |
|---|---|---|---|
| **Nonspecific PDE inhibitor**<br>Theophylline | ↓ cAMP hydrolysis → ↑ cAMP → bronchial smooth muscle relaxation → bronchodilation | COPD/asthma (rarely used) | Cardiotoxicity (eg, tachycardia, arrhythmia), neurotoxicity (eg, seizures, headache), abdominal pain |
| **PDE-5 inhibitors**<br>Sildena**fil**, vardena**fil**, tadala**fil**, avana**fil** | ↓ hydrolysis of cGMP → ↑ cGMP → ↑ smooth muscle relaxation by enhancing NO activity → pulmonary vasodilation and ↑ blood flow in corpus cavernosum **fil**ls the penis | Erectile dysfunction<br>Pulmonary hypertension<br>Benign pros**ta**tic hyperplasia (**ta**dalafil only) | Facial flushing, headache, dyspepsia, hypotension in patients taking nitrates; "**h**ot and sweaty," then **h**eadache, **h**eartburn, **h**ypotension<br>**S**ildenafil only: cyanopia (blue-tinted vision) via inhibition of PDE-6 (**s**ix) in retina |
| **PDE-4 inhibitor**<br>Roflumilast | ↑ cAMP in neutrophils, granulocytes, and bronchial epithelium | Severe COPD | Abdominal pain, weight loss, depression, anxiety, insomnia |
| **PDE-3 inhibitor**<br>Milrinone | In cardiomyocytes: ↑ cAMP → ↑ $Ca^{2+}$ influx → ↑ ionotropy and chronotropy<br>In vascular smooth muscle: ↑ cAMP → MLCK inhibition → vasodilation → ↓ preload and afterload | Acute decompensated HF with cardiogenic shock (inotrope) | Tachycardia, ventricular arrhythmias, hypotension |
| **"Platelet inhibitors"**<br>Cilostazol[a]<br>Dipyridamole[b] | In platelets: ↑ cAMP → inhibition of platelet aggregation | Intermittent claudication<br>Stroke or TIA prevention (with aspirin)<br>Cardiac stress testing (dipyridamole only, due to coronary vasodilation)<br>Prevention of coronary stent restenosis | Nausea, headache, facial flushing, hypotension, abdominal pain |

[a]Cilostazol is a PDE-3 inhibitor, but due to its indications is categorized as a platelet inhibitor together with dipyridamole.
[b]Dipyridamole is a nonspecific PDE inhibitor, leading to inhibition of platelet aggregation. It also prevents adenosine reuptake by platelets → ↑ extracellular adenosine → ↑ vasodilation.

## ▶ PHARMACOLOGY—TOXICITIES AND SIDE EFFECTS

**Ingested seafood toxins** Toxin actions include histamine release, total block of $Na^+$ channels, or opening of $Na^+$ channels to cause depolarization.

| TOXIN | SOURCE | ACTION | SYMPTOMS | TREATMENT |
|---|---|---|---|---|
| **Histamine (scombroid poisoning)** | Spoiled dark-meat fish such as tuna, mahi-mahi, mackerel, and bonito | Bacterial histidine decarboxylase converts histidine to histamine<br>Frequently misdiagnosed as fish allergy | Mimics anaphylaxis: oral burning sensation, facial flushing, erythema, urticaria, itching; may progress to bronchospasm, angioedema, hypotension | Antihistamines<br>Albuterol +/– epinephrine |
| **Tetrodotoxin** | Pufferfish | Binds fast voltage-gated $Na^+$ channels in nerve tissue, preventing depolarization | Nausea, diarrhea, paresthesias, weakness, dizziness, loss of reflexes | Supportive |
| **Ciguatoxin** | Reef fish such as barracuda, snapper, and moray eel | Opens $Na^+$ channels, causing depolarization | Nausea, vomiting, diarrhea; perioral numbness; reversal of hot and cold sensations; bradycardia, heart block, hypotension | Supportive |

**Age-related changes in pharmacokinetics** It's how aging bodies are **MADE**.

**Metabolism** ↓ hepatic mass, ↓ hepatic blood flow and ↓ drug metabolism.
Phase I metabolism lost first with aging. Drugs metabolized during phase II (eg, lorazepam, acetaminophen) are safer than drugs metabolized during phase I (eg, diazepam). Thus ↓ therapeutic doses may suffice in elderly.

**Absorption** ↑ gastric pH, ↓ gastric emptying.
Drug absorption influenced via drug-drug/food interactions.

**Distribution** ↑ body fat content (↑ $V_d$ for lipophilic drugs, eg, propofol).
↓ albumin (↓ binding of acidic drugs).
↓ total body water (↓ $V_d$ for hydrophilic drugs, eg, digoxin).

**Elimination** ↓ GFR and ↓ tubular secretion.
↑ plasma concentration of renally excreted drugs; thus ↓ therapeutic doses may suffice in elderly.

**Beers criteria** Widely used criteria developed to reduce potentially inappropriate prescribing and harmful polypharmacy in the geriatric population. Includes > 50 medications that should be avoided in elderly patients due to ↓ efficacy and/or ↑ risk of adverse events. Examples:
- α-blockers (↑ risk of hypotension)
- Anticholinergics, antidepressants, antihistamines, opioids (↑ risk of delirium, sedation, falls, constipation, urinary retention)
- Benzodiazepines (↑ risk of delirium, sedation, falls)
- NSAIDs (↑ risk of GI bleeding, especially with concomitant anticoagulation)
- PPIs (↑ risk of C *difficile* infection)

## Specific toxicity treatments

| TOXIN | TREATMENT |
|---|---|
| Acetaminophen | N-acetylcysteine (replenishes glutathione) |
| AChE inhibitors, organophosphates | Atropine > pralidoxime |
| Antimuscarinic, anticholinergic agents | Physostigmine (crosses BBB), control hyperthermia |
| Arsenic | Dimercaprol, succimer |
| Benzodiazepines | Flumazenil |
| β-blockers | Atropine, glucagon, saline |
| Carbon monoxide | 100% $O_2$, hyperbaric $O_2$ |
| **Copper** | "**Penny**"cillamine (penicillamine), **tri**entine (**3 copper penn**ies) |
| Cyanide | Hydroxocobalamin, nitrites + sodium thiosulfate |
| Dabigatran | Idarucizumab |
| Digoxin | Digoxin-specific antibody fragments |
| Direct factor Xa inhibitors (eg, apixaban) | Andexanet alfa |
| Heparin | Protamine sulfate |
| Iron (**Fe**) | De**fe**roxamine, de**fe**rasirox, de**fe**riprone |
| Lead | Calcium disodium EDTA, dimercaprol, succimer, penicillamine |
| **Mer**cury | Di**mer**caprol, succi**mer** |
| Methanol, ethylene glycol (antifreeze) | Fomepizole > ethanol, dialysis |
| **Meth**emoglobin | **Meth**ylene blue, vitamin C (reducing agent) |
| Methotrexate | Leucovorin |
| **O**pi**o**ids | Nal**o**x**o**ne |
| Salicylates | $NaHCO_3$ (alkalinize urine), dialysis |
| TCAs | $NaHCO_3$ (stabilizes cardiac cell membrane) |
| Warfarin | Vitamin K (delayed effect), PCC (prothrombin complex concentrate)/FFP (immediate effect) |

## Drug reactions—cardiovascular

| DRUG REACTION | CAUSAL AGENTS |
|---|---|
| Coronary vasospasm | **C**ocaine, **A**mphetamines, **S**umatriptan, **E**rgot alkaloids (**CASE**) |
| Cutaneous flushing | **V**ancomycin, **A**denosine, **N**iacin, **C**a$^{2+}$ channel blockers, **E**chinocandins, **N**itrates (**flush**ed from **VANCEN** [dancing])<br>Red man syndrome—rate-dependent infusion reaction to vancomycin causing widespread pruritic erythema due to histamine release. Manage with diphenhydramine, slower infusion rate. |
| Dilated cardiomyopathy | Alcohol, anthracycline (eg, **d**oxorubicin, **d**aunorubicin; prevent with **d**exrazoxane), trastuzumab |
| Torsades de pointes | Agents that prolong QT interval: anti**A**rrhythmics (class IA, III), anti**B**iotics (eg, macrolides, fluoroquinolones), anti"**C**"ychotics (eg, ziprasidone), anti**D**epressants (eg, TCAs), anti**E**metics (eg, ondansetron), anti**F**ungals (eg, fluconazole) (**ABCDEF**) |

### Drug reactions—endocrine/reproductive

| DRUG REACTION | CAUSAL AGENTS | NOTES |
|---|---|---|
| Adrenocortical insufficiency | HPA suppression 2° to glucocorticoid withdrawal | |
| Diabetes insipidus | Lithium, demeclocycline | |
| Gynecomastia | Ketoconazole, cimetidine, spironolactone, GnRH analogs/antagonists, androgen receptor inhibitors, 5α-reductase inhibitors | |
| Hot flashes | SERMs (eg, tamoxifen, clomiphene, raloxifene) | |
| Hyperglycemia | **T**acrolimus, **p**rotease inhibitors, **n**iacin, **H**CTZ, **c**orticosteroids | **T**he **p**eople **n**eed **h**ard **c**andies |
| Hyperprolactinemia | Typical antipsychotics (eg, haloperidol), atypical antipsychotics (eg, risperidone), metoclopramide, methyldopa, reserpine | Presents with hypogonadism (eg, infertility, amenorrhea, erectile dysfunction) and galactorrhea |
| Hyperthyroidism | Amiodarone, iodine, lithium | |
| Hypothyroidism | **Am**iodarone, **l**ithium | I **am** **l**ethargic |
| SIADH | **C**arbamazepine, **C**yclophosphamide, **SS**RIs | **C**an't **C**oncentrate **S**erum **S**odium |

### Drug reactions—gastrointestinal

| DRUG REACTION | CAUSAL AGENTS | NOTES |
|---|---|---|
| Acute cholestatic hepatitis, jaundice | Macrolides (eg, erythromycin) | |
| Diarrhea | Acamprosate, antidiabetic agents (acarbose, metformin, pramlintide), colchicine, cholinesterase inhibitors, lipid-lowering agents (eg, ezetimibe, orlistat), macrolides (eg, erythromycin), SSRIs, chemotherapy (eg, irinotecan) | |
| Focal to massive hepatic necrosis | **H**alothane, ***A**manita phalloides* (death cap mushroom), **v**alproic acid, **ac**etaminophen | Liver "**hAvac**" |
| Hepatitis | Rifampin, isoniazid, pyrazinamide, statins, fibrates | |
| Pancreatitis | **D**idanosine, **c**orticosteroids, **a**lcohol, **v**alproic acid, **a**zathioprine, **d**iuretics (eg, furosemide, HCTZ) | **D**rugs **c**ausing **a** **v**iolent **a**bdominal **d**istress |
| Pill-induced esophagitis | Bisphosphonates, ferrous sulfate, NSAIDs, potassium chloride, tetracyclines | Usually occurs at anatomic sites of esophageal narrowing (eg, near level of aortic arch); caustic effect minimized with upright posture and adequate water ingestion |
| Pseudomembranous colitis | Ampicillin, cephalosporins, clindamycin, fluoroquinolones, PPIs | Antibiotics predispose to superinfection by resistant C *difficile* |

### Drug reactions—hematologic

| DRUG REACTION | CAUSAL AGENTS | NOTES |
|---|---|---|
| Agranulocytosis | Dapsone, clozapine, carbamazepine, propylthiouracil, methimazole, colchicine, ticlopidine, ganciclovir | Drugs can cause pretty major collapse to granulocytes |
| Aplastic anemia | Carbamazepine, methimazole, NSAIDs, benzene, chloramphenicol, propylthiouracil | Can't make New blood cells properly |
| Direct Coombs ⊕ hemolytic anemia | Penicillin, methylDopa, Cephalosporins | P Diddy Coombs |
| Drug reaction with eosinophilia and systemic symptoms[a] | Allopurinol, antiBiotics, antiConvulsants, sulfa drugs | ABCs |
| Gray baby syndrome | Chloramphenicol | |
| Hemolysis in G6PD deficiency | Isoniazid, sulfonamides, dapsone, primaquine, aspirin, ibuprofen, nitrofurantoin | Hemolysis is d pain |
| Megaloblastic anemia | Hydroxyurea, Phenytoin, Methotrexate, Sulfa drugs | You're having a mega blast with PMS |
| Thrombocytopenia | Indinavir, heparin, quinidine, ganciclovir, vancomycin, linezolid, abciximab | I have quickly gotten very low amounts |
| Thrombotic complications | Combined oral contraceptives, hormone replacement therapy, SERMs, epoetin alfa | Estrogen-mediated adverse effect |

[a]DRESS is a delayed hypersensitivity reaction associated with latent herpesvirus reactivation. Latency period (2–8 weeks), then fever, morbilliform skin rash, multiorgan involvement. Treatment: withdrawal of offending drug, corticosteroids

### Drug reactions—musculoskeletal/skin/connective tissue

| DRUG REACTION | CAUSAL AGENTS | NOTES |
|---|---|---|
| Drug-induced lupus | Methyldopa, minocycline, hydralazine, isoniazid, phenytoin, sulfa drugs, etanercept, procainamide | Lupus makes my hips extremely painful |
| Fat redistribution | Protease inhibitors, glucocorticoids | Fat protects glutes |
| Gingival hyperplasia | Cyclosporine, $Ca^{2+}$ channel blockers, phenytoin | Can Cause puffy gums |
| Hyperuricemia (gout) | Pyrazinamide, thiazides, furosemide, niacin, cyclosporine | Painful tophi and feet need care |
| Myopathy | Statins, fibrates, niacin, colchicine, daptomycin, hydroxychloroquine, interferon-α, penicillamine, glucocorticoids | |
| Osteoporosis | Corticosteroids, depot medroxyprogesterone acetate, GnRH agonists, aromatase inhibitors, anticonvulsants, heparin, PPIs | |
| Photosensitivity | Sulfonamides, amiodarone, tetracyclines, 5-FU | Sat For photo |
| Rash (Stevens-Johnson syndrome) | Anti-epileptic drugs (especially lamotrigine), allopurinol, sulfa drugs, penicillin | Steven Johnson has epileptic allergy to sulfa drugs and penicillin |
| Teeth discoloration | Tetracyclines | Teethracyclines |
| Tendon/cartilage damage | Fluoroquinolones | |

### Drug reactions—neurologic

| DRUG REACTION | CAUSAL AGENTS | NOTES |
|---|---|---|
| Cinchonism | Quinidine, quinine | Can present with tinnitus, hearing/vision loss, psychosis, and cognitive impairment |
| Parkinson-like syndrome | **A**ntipsychotics, **r**eserpine, **m**etoclopramide | Cogwheel rigidity of **arm** |
| Peripheral neuropathy | Isoniazid, phenytoin, platinum agents (eg, cisplatin), paclitaxel, vincristine | |
| Idiopathic intracranial hypertension | Vitamin **A**, **g**rowth **h**ormones, **t**etracyclines | **A**lways **g**row **h**ead **t**ension |
| Seizures | **I**soniazid, **b**upropion, **i**mipenem/cilastatin, **t**ramadol, **e**nflurane | With **seizures**, **I bite** my tongue |
| Tardive dyskinesia | Antipsychotics, metoclopramide | |
| Visual disturbance | **T**opiramate (blurred vision/diplopia, haloes), **h**ydroxychloroquine (↓ visual acuity, visual field defects), **d**igoxin (yellow-tinged vision), **i**soniazid (optic neuritis), **v**igabatrin (visual field defects), **P**DE-5 inhibitors (blue-tinged vision), **e**thambutol (color vision changes) | **T**hese **h**orrible **d**rugs **i**rritate **v**ery **P**recious **e**yes |

### Drug reactions—renal/genitourinary

| DRUG REACTION | CAUSAL AGENTS | NOTES |
|---|---|---|
| Fanconi syndrome | Cisplatin, ifosfamide, expired tetracyclines, tenofovir | |
| Hemorrhagic cystitis | Cyclophosphamide, ifosfamide | Prevent by coadministering with mesna |
| Interstitial nephritis | Diuretics (**P**ee), NSAIDs (**P**ain-free), **P**enicillins and cephalosporins, **P**PIs, rifam**P**in, **s**ulfa drugs | Remember the **5 P's** |

### Drug reactions—respiratory

| DRUG REACTION | CAUSAL AGENTS | NOTES |
|---|---|---|
| Dry cough | ACE inhibitors | |
| Pulmonary fibrosis | **M**ethotrexate, **n**itrofurantoin, **c**armustine, **b**leomycin, **b**usulfan, **a**miodarone | **M**y **n**ose **c**annot **b**reathe **b**ad **a**ir |

### Drug reactions—multiorgan

| DRUG REACTION | CAUSAL AGENTS | NOTES |
|---|---|---|
| Antimuscarinic | Atropine, TCAs, $H_1$-blockers, antipsychotics | |
| Disulfiram-like reaction | 1st-generation **s**ulfonylureas, **p**rocarbazine, certain **c**ephalosporins, **g**riseofulvin, **m**etronidazole | **S**orry **p**als, **c**an't **g**o **m**ingle |
| Nephrotoxicity/ototoxicity | **L**oop diuretics, **c**isplatin, **a**minoglycosides, **a**mphotericin, **vancomycin** | **L**isten **Cis**! **A**lways **a**djust **vancomycin** in CKD. Cisplatin toxicity may respond to amifostine |

**Drugs affecting pupil size**

| ↑ pupil size (mydriasis) | ↓ pupil size (miosis) |
|---|---|
| Anticholinergics (eg, atropine, TCAs, tropicamide, scopolamine, antihistamines) | Sympatholytics (eg, $\alpha_2$-agonists) |
| Indirect sympathomimetics (eg, amphetamines, cocaine, LSD), meperidine | Opioids (except meperidine) |
| Direct sympathomimetics | Parasympathomimetics (eg, pilocarpine), organophosphates |

**Cytochrome P-450 interactions (selected)**

| Inducers (+) | Substrates | Inhibitors (–) |
|---|---|---|
| St. John's wort<br>Griseofulvin<br>Carbamazepine<br>Chronic alcohol overuse<br>Rifampin<br>Modafinil<br>Nevirapine<br>Phenytoin<br>Phenobarbital | Theophylline<br>OCPs<br>Anti-epileptics<br>Warfarin | Sodium valproate<br>Isoniazid<br>Cimetidine<br>Ketoconazole<br>Fluconazole<br>Acute alcohol overuse<br>Chloramphenicol<br>Erythromycin/clarithromycin<br>Sulfonamides<br>Ciprofloxacin<br>Omeprazole<br>Metronidazole<br>Amiodarone<br>Ritonavir<br>Grapefruit juice |
| St. John grimaced at the carbs in chronic alcohol overuse, refused more, and never again forgot his phen-phen | The OCPs are anti-war | SICKFACES.COM (when I am really drinking grapefruit juice) |

**Sulfa drugs**

Sulfonamide antibiotics, Sulfasalazine, Probenecid, Furosemide, Acetazolamide, Celecoxib, Thiazides, Sulfonylureas.

Patients with sulfa allergies may develop fever, urinary tract infection, Stevens-Johnson syndrome, hemolytic anemia, thrombocytopenia, agranulocytosis, acute interstitial nephritis, and urticaria (hives).

Scary Sulfa Pharm FACTS

## ▶ PHARMACOLOGY—MISCELLANEOUS

### Drug names

| ENDING | CATEGORY | EXAMPLE |
|---|---|---|
| **Antimicrobial** | | |
| **-asvir** | NS5A inhibitor | Ledipasvir |
| **-bendazole** | Antiparasitic/antihelminthic | Mebendazole |
| **-buvir** | NS5B inhibitor | Sofosbuvir |
| **-cillin** | Transpeptidase inhibitor | Ampicillin |
| **-conazole** | Ergosterol synthesis inhibitor | Ketoconazole |
| **-cycline** | Protein synthesis inhibitor | Tetracycline |
| **-floxacin** | Fluoroquinolone | Ciprofloxacin |
| **-mivir** | Neuraminidase inhibitor | Oseltamivir |
| **-navir** | Protease inhibitor | Ritonavir |
| **-ovir** | Viral DNA polymerase inhibitor | Acyclovir |
| **-previr** | NS3/4A inhibitor | Simeprevir |
| **-tegravir** | Integrase inhibitor | Elvitegravir |
| **-thromycin** | Macrolide | Azithromycin |
| **Antineoplastic** | | |
| **-case** | Recombinant uricase | Rasburicase |
| **-mustine** | Nitrosourea | Carmustine |
| **-platin** | Platinum compound | Cisplatin |
| **-poside** | Topoisomerase II inhibitor | Etoposide |
| **-rubicin** | Anthracycline | Doxorubicin |
| **-taxel** | Taxane | Paclitaxel |
| **-tecan** | Topoisomerase I inhibitor | Irinotecan |
| **CNS** | | |
| **-ane** | Inhaled anesthetic | Halothane |
| **-apine, -idone** | Atypical antipsychotic | Quetiapine, risperidone |
| **-azine** | Typical antipsychotic | Thioridazine |
| **-barbital** | Barbiturate | Phenobarbital |
| **-benazine** | VMAT inhibitor | Tetrabenazine |
| **-caine** | Local anesthetic | Lidocaine |
| **-capone** | COMT inhibitor | Entacapone |
| **-curium, -curonium** | Nondepolarizing neuromuscular blocker | Atracurium, pancuronium |
| **-giline** | MAO-B inhibitor | Selegiline |
| **-ipramine, -triptyline** | TCA | Imipramine, amitriptyline |
| **-triptan** | 5-$HT_{1B/1D}$ agonist | Sumatriptan |
| **-zepam, -zolam** | Benzodiazepine | Diazepam, alprazolam |

### Drug names *(continued)*

| ENDING | CATEGORY | EXAMPLE |
|---|---|---|
| **Autonomic** | | |
| **-chol** | Cholinergic agonist | Bethanechol |
| **-olol** | $\beta$-blocker | Propranolol |
| **-stigmine** | AChE inhibitor | Neostigmine |
| **-terol** | $\beta_2$-agonist | Albuterol |
| **-zosin** | $\alpha_1$-blocker | Prazosin |
| **Cardiovascular** | | |
| **-afil** | PDE-5 inhibitor | Sildenafil |
| **-dipine** | Dihydropyridine $Ca^{2+}$ channel blocker | Amlodipine |
| **-parin** | Low-molecular-weight heparin | Enoxaparin |
| **-plase** | Thrombolytic | Alteplase |
| **-pril** | ACE inhibitor | Captopril |
| **-sartan** | Angiotensin-II receptor blocker | Losartan |
| **-xaban** | Direct factor Xa inhibitor | Apixaban |
| **Metabolic** | | |
| **-gliflozin** | SGLT-2 inhibitor | Dapagliflozin |
| **-glinide** | Meglitinide | Repaglinide |
| **-gliptin** | DPP-4 inhibitor | Sitagliptin |
| **-glitazone** | PPAR-$\gamma$ activator | Rosiglitazone |
| **-glutide** | GLP-1 analog | Liraglutide |
| **-statin** | HMG-CoA reductase inhibitor | Lovastatin |
| **Other** | | |
| **-caftor** | CFTR modulator | Lumacaftor |
| **-dronate** | Bisphosphonate | Alendronate |
| **-lukast** | CysLT1 receptor blocker | Montelukast |
| **-lutamide** | Androgen receptor inhibitor | Flutamide |
| **-pitant** | $NK_1$ blocker | Aprepitant |
| **-prazole** | Proton pump inhibitor | Omeprazole |
| **-prost** | Prostaglandin analog | Latanoprost |
| **-sentan** | Endothelin receptor antagonist | Bosentan |
| **-setron** | 5-$HT_3$ blocker | Ondansetron |
| **-steride** | 5$\alpha$-reductase inhibitor | Finasteride |
| **-tadine** | $H_1$-antagonist | Loratadine |
| **-tidine** | $H_2$-antagonist | Cimetidine |
| **-trozole** | Aromatase inhibitor | Anastrozole |
| **-vaptan** | ADH antagonist | Tolvaptan |

### Biologic agents

| ENDING | CATEGORY | EXAMPLE |
|---|---|---|
| **Monoclonal antibodies (-mab)—target overexpressed cell surface receptors** | | |
| -ximab | Chimeric human-mouse monoclonal antibody | Rituximab |
| -zumab | Humanized monoclonal antibody | Bevacizumab |
| -umab | Human monoclonal antibody | Denosumab |
| **Small molecule inhibitors (-ib)—target intracellular molecules** | | |
| -ciclib | Cyclin-dependent kinase inhibitor | Palbociclib |
| -coxib | COX-2 inhibitor | Celecoxib |
| -parib | Poly(ADP-ribose) polymerase inhibitor | Olaparib |
| -rafenib | BRAF inhibitor | Vemurafenib |
| -tinib | Tyrosine kinase inhibitor | Imatinib |
| -zomib | Proteasome inhibitor | Bortezomib |
| **Receptor fusion proteins (-cept)** | | |
| -cept | TNF-α antagonist | Etanercept |
| **Interleukin receptor modulators (-kin)—agonists and antagonists of interleukin receptors** | | |
| -leukin | Interleukin-2 agonist/analog | Aldesleukin |
| -kinra | Interleukin receptor antagonist | Anakinra |

HIGH-YIELD PRINCIPLES IN

# Public Health Sciences

*"Medicine is a science of uncertainty and an art of probability."*

—Sir William Osler

*"Whenever a doctor cannot do good, he must be kept from doing harm."*

—Hippocrates

*"On a long enough timeline, the survival rate for everyone drops to zero."*

—Chuck Palahniuk, *Fight Club*

*"Of all forms of discrimination and inequalities, injustice in health is the most shocking and inhuman."*

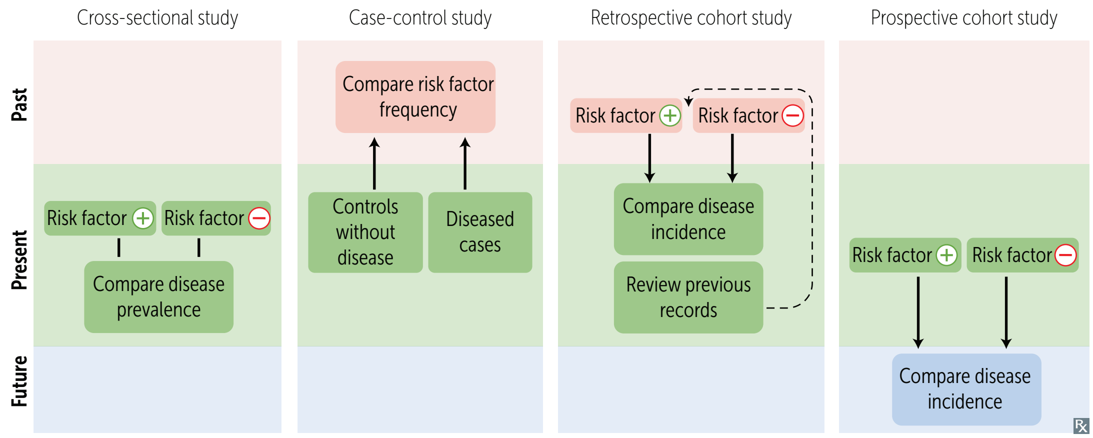
—Martin Luther King, Jr.

A heterogenous mix of epidemiology, biostatistics, ethics, law, healthcare delivery, patient safety, quality improvement, and more falls under the heading of public health sciences. Biostatistics and epidemiology are the foundations of evidence-based medicine and are very high yield. Make sure you can quickly apply biostatistical equations such as sensitivity, specificity, and predictive values in a problem-solving format. Also, know how to set up your own 2 × 2 tables, and beware questions that switch the columns. Quality improvement and patient safety topics were introduced a few years ago on the exam and represent trends in health system science. Medical ethics questions often require application of principles. Typically, you are presented with a patient scenario and then asked how you would respond. For this edition, we have added a section on communication skills given their growing emphasis on the exam. Effective communication is essential to the physician-patient partnership. Physicians must seek opportunities to connect with patients, understand their perspectives, express empathy, and form shared decisions and realistic goals.

## ▶ PUBLIC HEALTH SCIENCES—EPIDEMIOLOGY AND BIOSTATISTICS

### Observational studies

| STUDY TYPE | DESIGN | MEASURES/EXAMPLE |
|---|---|---|
| **Case series** | Describes several individual patients with the same diagnosis, treatment, or outcome. | Description of clinical findings and symptoms. Has no comparison group, thus cannot show risk factor association with disease. |
| **Cross-sectional study** | Frequency of disease and frequency of risk-related factors are assessed in the present. Asks, "What is happening?" | Disease prevalence. Can show risk factor association with disease, but does not establish causality. |
| **Case-control study** | Retrospectively compares a group of people with disease to a group without disease. Looks to see if odds of prior exposure or risk factor differ by disease state. Asks, "What happened?" | Odds ratio (**OR**). **Control** the case in the **OR**. Patients with COPD had higher odds of a smoking history than those without COPD. |
| **Cohort study** | Compares a group with a given exposure or risk factor to a group without such exposure. Looks to see if exposure or risk factor is associated with later development of disease. Can be prospective or retrospective. | Disease incidence. Relative risk (RR). People who smoke had a higher risk of developing COPD than people who do not. Coho**rt** = **r**ela**t**ive risk. |
| **Twin concordance study** | Compares the frequency with which both monozygotic twins vs both dizygotic twins develop the same disease. | Measures heritability and influence of environmental factors ("nature vs nurture"). |
| **Adoption study** | Compares siblings raised by biological vs adoptive parents. | Measures heritability and influence of environmental factors. |
| **Ecological study** | Compares frequency of disease and frequency of risk-related factors across populations. Measures population data not necessarily applicable to individuals (ecological fallacy). | Used to monitor population health. COPD prevalence was higher in more polluted cities. |



| | |
|---|---|
| **Clinical trial** | Experimental study involving humans. Compares therapeutic benefits of ≥2 treatments, or of treatment and placebo. Study quality improves when study is randomized, controlled, and double-blinded (ie, neither patient nor researcher knows whether the patient is in the treatment or control group). Triple-blind refers to the additional blinding of the researchers analyzing the data. Five phases ("Can **I SWIM**?"). |
| **Crossover study** | Compares the effect of a series of ≥2 treatments on a participant. Order in which participants receive treatments is randomized. Washout period occurs between treatments.<br>Allows participants to serve as own controls.<br>Intention-to-treat analysis: All patients are analyzed according to their original, randomly assigned treatment. No patients are excluded. Attempts to avoid misleading bias from patients dropping out.<br>Per protocol analysis: Only patients who complete the study "per protocol" are included in analysis. Patients who fail to complete treatment as originally, randomly assigned are excluded. Risk of bias from non-random noncompliance. |

| DRUG TRIALS | TYPICAL STUDY SAMPLE | PURPOSE |
|---|---|---|
| **Phase 0** | Very small number of either healthy volunteers or patients with disease of interest. | **I**nitial pharmocokinetic and pharmacodynamic assessment. Uses <1% of therapeutic dose. No safety or toxicity assessment. |
| **Phase I** | Small number of either healthy volunteers or patients with disease of interest; more than Phase 0. | "Is it **S**afe?" Assesses safety, toxicity, dosage, pharmacokinetics, and pharmacodynamics. |
| **Phase II** | Moderate number of patients with disease of interest. | "Does it **W**ork?" Assesses treatment efficacy, and adverse effects. |
| **Phase III** | Large number of patients with disease of interest randomly assigned either to the treatment under investigation or to the standard of care (or placebo). | "Is it as good or better?" Compares the new treatment to the current standard of care (any **I**mprovement?). |
| **Phase IV** | Postmarketing surveillance of patients after treatment is approved. | "Can it stay on the **M**arket?" Detects rare or long-term adverse effects and evaluates cost-effectiveness. |

| | |
|---|---|
| **Bradford Hill criteria** | A group of principles that provide limited support for establishing evidence of a causal relationship between presumed cause and effect. |
| **Strength** | Association does not imply causation, but the stronger the association, the more evidence for causation. |
| **Consistency** | Repeated observations of the findings in multiple distinct samples. |
| **Specificity** | The more specific the presumed cause is to the effect, the stronger the evidence for causation. |
| **Temporality** | The presumed cause precedes the effect by an expected amount of time. |
| **Biological gradient** | Greater effect observed with greater exposure to the presumed cause (dose-response relationship). |
| **Plausibility** | A conceivable mechanism exists by which the cause may lead to the effect. |
| **Coherence** | The presumed cause and effect do not conflict with existing scientific consensus. |
| **Experiment** | Empirical evidence supporting the presumed cause and effect (eg, animal studies, in vitro studies). |
| **Analogy** | The presumed cause and effect are comparable to a similar, established cause and effect. |

## Quantifying risk

Definitions and formulas are based on the classic 2 × 2 or contingency table.

| Exposure or intervention | Disease or outcome ⊕ | Disease or outcome ⊖ |
|---|---|---|
| ⊕ | a | b |
| ⊖ | c | d |

| TERM | DEFINITION | EXAMPLE | FORMULA |
|---|---|---|---|
| **Odds ratio** | Typically used in case-control studies. Represents the odds of exposure among cases (a/c) vs odds of exposure among controls (b/d).<br>OR = 1 → odds of exposure are equal in cases and controls.<br>OR > 1 → odds of exposure are greater in cases.<br>OR < 1 → odds of exposure are greater in controls. | If in a case-control study, 20/30 patients with lung cancer and 5/25 healthy individuals report smoking, the OR is 8; so the patients with lung cancer are 8 times more likely to have a history of smoking. | $OR = \frac{a/c}{b/d} = \frac{ad}{bc}$<br>$\begin{array}{|c|c|} \hline a\ 20 & b\ 5 \\ \hline c\ 10 & d\ 20 \\ \hline \end{array}$ |
| **Relative risk** | Typically used in cohort studies. Risk of developing disease in the exposed group divided by risk in the unexposed group.<br>RR = 1 → no association between exposure and disease.<br>RR > 1 → exposure associated with ↑ disease occurrence.<br>RR < 1 → exposure associated with ↓ disease occurrence. | If 5/10 people exposed to radiation are diagnosed with cancer, and 1/10 people not exposed to radiation are diagnosed with cancer, the RR is 5; so people exposed to radiation have a 5 times greater risk of developing cancer.<br>For rare diseases (low prevalence), OR approximates RR. | $RR = \frac{a/(a+b)}{c/(c+d)}$<br>$\begin{array}{|c|c|} \hline a\ 5 & b\ 5 \\ \hline c\ 1 & d\ 9 \\ \hline \end{array}$ |
| **Relative risk reduction** | The proportion of risk reduction attributable to the intervention as compared to a control. | If 2% of patients who receive a flu shot develop the flu, while 8% of unvaccinated patients develop the flu, then RR = 2/8 = 0.25, and RRR = 0.75. | $RRR = 1 - RR$ |
| **Attributable risk** | The difference in risk between exposed and unexposed groups. | If risk of lung cancer in people who smoke is 21% and risk in people who don't smoke is 1%, then the attributable risk is 20%. | $AR = \frac{a}{a+b} - \frac{c}{c+d}$<br>$AR\% = \frac{RR-1}{RR} \times 100$ |
| **Absolute risk reduction** | The difference in risk (not the proportion) attributable to the intervention as compared to a control. | If 8% of people who receive a placebo vaccine develop the flu vs 2% of people who receive a flu vaccine, then ARR = 8%–2% = 6% = 0.06. | $ARR = \frac{c}{c+d} - \frac{a}{a+b}$ |
| **Number needed to treat** | Number of patients who need to be treated for 1 patient to benefit. Lower number = better treatment. | | NNT = 1/ARR |
| **Number needed to harm** | Number of patients who need to be exposed to a risk factor for 1 patient to be harmed. Higher number = safer exposure. | | NNH = 1/**AR** |
| **Case fatality rate** | Percentage of deaths occurring among those with disease. | If 4 patients die among 10 cases of meningitis, case fatality rate is 40%. | $CFR\% = \frac{\text{deaths}}{\text{cases}} \times 100$ |

**Quantifying risk *(continued)***

| TERM | DEFINITION | EXAMPLE | FORMULA |
|---|---|---|---|
| **Mortality rate** | Number of deaths (in general or due to specific cause) within a population over a period, typically scaled to deaths per 1000 people per year. | If 80 people in a town of 10,000 die over 2 years, mortality rate is 4 per 1000 per year. | |
| **Attack rate** | Proportion of exposed people who become ill. | If 80 people in a town are exposed and 60 people become ill, attack rate is 75%. | $\frac{\text{People who become ill}}{\text{Total people exposed}}$ |

**Likelihood ratio**

$$LR^{+} = \frac{\text{probability of positive result in patient with disorder}}{\text{probability of positive result in patient without disorder}} = \frac{\text{sensitivity}}{1 - \text{specificity}} = \frac{\text{TP rate}}{\text{FP rate}}$$

$$LR^{-} = \frac{\text{probability of negative result in patient with disorder}}{\text{probability of negative result in patient without disorder}} = \frac{1 - \text{sensitivity}}{\text{specificity}} = \frac{\text{FN rate}}{\text{TN rate}}$$

$LR^{+} > 10$ indicates a highly specific test, while $LR^{-} < 0.1$ indicates a highly sensitive test.

### Evaluation of diagnostic tests

Sensitivity and specificity are fixed properties of a test. PPV and NPV vary depending on disease prevalence in population being tested.

| Test \ Disease | ⊕ | ⊖ | |
|---|---|---|---|
| ⊕ | TP | FP | PPV = TP/(TP + FP) |
| ⊖ | FN | TN | NPV = TN/(TN + FN) |
| | Sensitivity = TP/(TP + FN) | Specificity = TN/(TN + FP) | Prevalence $\frac{TP + FN}{(TP + FN + FP + TN)}$ |

### Sensitivity (true-positive rate)

Proportion of all people with disease who test positive, or the ability of a test to correctly identify those with the disease.
Value approaching 100% is desirable for **ruling out** disease and indicates a **low false-negative rate**.

= TP / (TP + FN)
= 1 – FN rate
**SN-N-OUT** = highly **S**e**N**sitive test, when **N**egative, rules **OUT** disease
High sensitivity test used for screening

### Specificity (true-negative rate)

Proportion of all people without disease who test negative, or the ability of a test to correctly identify those without the disease.
Value approaching 100% is desirable for **ruling in** disease and indicates a **low false-positive rate**.

= TN / (TN + FP)
= 1 – FP rate
**SP-P-IN** = highly **SP**ecific test, when **P**ositive, rules **IN** disease
High specificity test used for confirmation after a positive screening test

### Positive predictive value

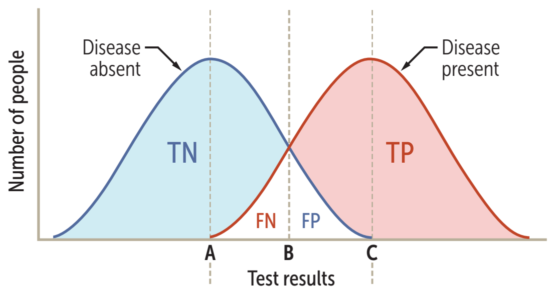
Probability that a person who has a positive test result actually has the disease.

PPV = TP / (TP + FP)
PPV varies directly with pretest probability (baseline risk, such as prevalence of disease): high pretest probability → high PPV

### Negative predictive value

Probability that a person with a negative test result actually does not have the disease.

NPV = TN / (TN + FN)
NPV varies inversely with prevalence or pretest probability

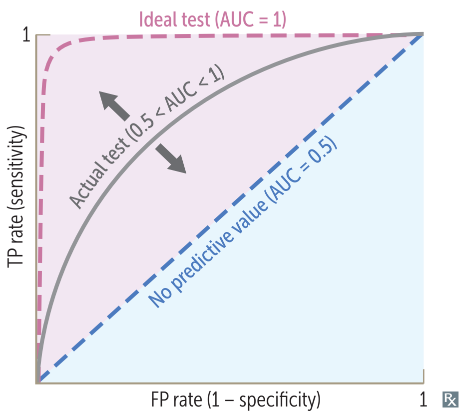



Possible cutoff values for ⊕ vs ⊖ test result
**A** = 100% sensitivity cutoff value
**B** = practical compromise between specificity and sensitivity
**C** = 100% specificity cutoff value

| | |
|---|---|
| Lowering the cutoff value: **B** → **A** (↑ FP ↓ FN) | ↑ Sensitivity ↑ NPV<br>↓ Specificity ↓ PPV |
| Raising the cutoff value: **B** → **C** (↑ FN ↓ FP) | ↑ Specificity ↑ PPV<br>↓ Sensitivity ↓ NPV |

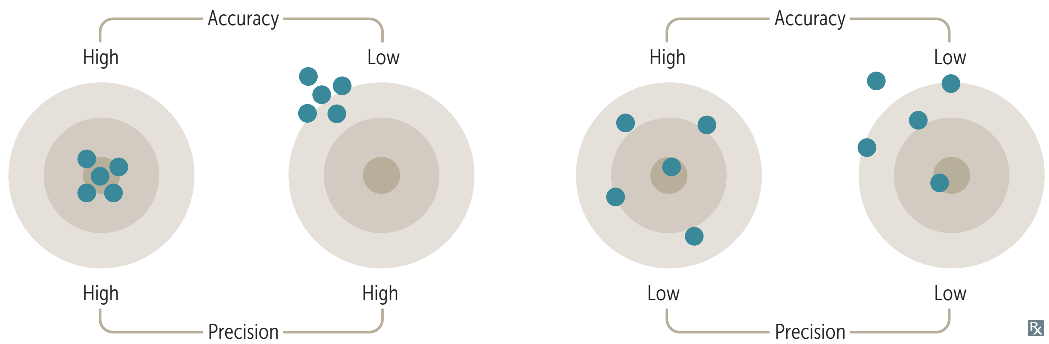
### Receiver operating characteristic curve

ROC curve demonstrates how well a diagnostic test can distinguish between 2 groups (eg, disease vs healthy). Plots the true-positive rate (sensitivity) against the false-positive rate (1 – specificity).
The better performing test will have a higher area under the curve (AUC), with the curve closer to the upper left corner.

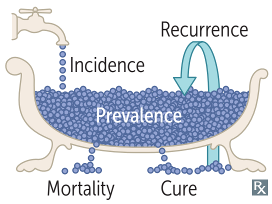


## Precision vs accuracy

| | | |
|---|---|---|
| **Precision (reliability)** | The consistency and reproducibility of a test. The absence of random variation in a test. | Random error ↓ precision in a test. ↑ precision → ↓ standard deviation. ↑ precision → ↑ statistical power ($1 - \beta$). |
| **Accuracy (validity)** | The closeness of test results to the true values. The absence of systematic error or bias in a test. | Systematic error ↓ accuracy in a test. |




## Incidence vs prevalence




$$\text{Incidence} = \frac{\text{\# of new cases}}{\text{\# of people at risk}} \quad \text{(per unit of time)}$$

**Incidence** looks at new cases (**incidents**).

$$\text{Prevalence} = \frac{\text{\# of existing cases}}{\text{Total \# of people in a population}} \quad \text{(at a point in time)}$$

Prevalence looks at **all** current cases.

$$\frac{\text{Prevalence}}{1 - \text{prevalence}} = \text{Incidence rate} \times \text{average duration of disease}$$

Prevalence ≈ incidence for short duration disease (eg, common cold).

Prevalence > incidence for chronic diseases, due to large # of existing cases (eg, diabetes).

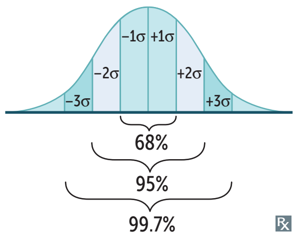
Prevalence ~ pretest probability.
↑ prevalence → ↑ PPV and ↓ NPV.

| SITUATION | INCIDENCE | PREVALENCE |
|---|---|---|
| ↑ survival time | — | ↑ |
| ↑ mortality | — | ↓ |
| Faster recovery time | — | ↓ |
| Extensive vaccine administration | ↓ | ↓ |
| ↓ risk factors | ↓ | ↓ |
| ↑ diagnostic sensitivity | ↑ | ↑ |

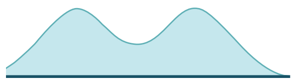
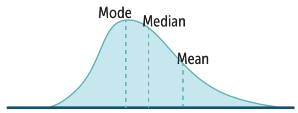
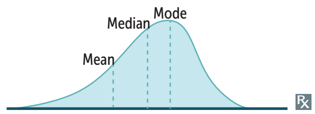
## Bias and study errors

| TYPE | DEFINITION | EXAMPLES | STRATEGIES TO REDUCE BIAS |
|---|---|---|---|
| **Recruiting participants** | | | |
| **Selection bias** | Nonrandom sampling or treatment allocation of subjects such that study population is not representative of target population<br>Most commonly a sampling bias | Berkson bias—cases and/or controls selected from hospitals (**be**dside **bias**) are less healthy and have different exposures<br>Attrition bias—participants lost to follow up have a different prognosis than those who complete the study | Randomization (creates groups with similar distributions of known and unknown variables)<br>Ensure the choice of the right comparison/reference group |
| **Performing study** | | | |
| **Recall bias** | Awareness of disorder alters recall by subjects; common in retrospective studies | Patients with disease recall exposure after learning of similar cases | Decrease time from exposure to follow-up |
| **Measurement bias** | Information is gathered in a systemically distorted manner | Using a faulty automatic sphygmomanometer<br>Hawthorne effect—participants change behavior upon awareness of being observed | Use objective, standardized, and previously tested methods of data collection that are planned ahead of time<br>Use placebo group |
| **Procedure bias** | Subjects in different groups are not treated the same | Patients in treatment group spend more time in highly specialized hospital units | Blinding (masking) and use of placebo reduce influence of participants and researchers on procedures and interpretation of outcomes as neither are aware of group assignments |
| **Observer-expectancy bias** | Researcher's belief in the efficacy of a treatment changes the outcome of that treatment (aka, Pygmalion effect) | An observer expecting treatment group to show signs of recovery is more likely to document positive outcomes | |
| **Interpreting results** | | | |
| **Confounding bias** | Factor related to both exposure and outcome (but not on causal path) distorts effect of exposure on outcome (vs effect modification, in which the exposure leads to different outcomes in subgroups stratified by the factor) | An uncontrolled study shows an association between drinking coffee and lung cancer; however, people who drink coffee may smoke more, which could account for the association | Multiple/repeated studies<br>Crossover studies (subjects act as their own controls)<br>Matching (patients with similar characteristics in both treatment and control groups) |
| **Lead-time bias** | Early detection interpreted as ↑ survival, but the disease course has not changed | Breast cancer diagnosed early by mammography may appear to exaggerate survival time because patients are known to have the cancer for longer | Measure "back-end" survival (adjust survival according to the severity of disease at the time of diagnosis) |
| **Length-time bias** | Screening test detects diseases with long latency period, while those with shorter latency period become symptomatic earlier | A slowly progressive cancer is more likely detected by a screening test than a rapidly progressive cancer | A randomized controlled trial assigning subjects to the screening program or to no screening |

## Statistical distribution

| | | |
|---|---|---|
| **Measures of central tendency** | Mean = (sum of values)/(total number of values). | Most affected by outliers (extreme values). |
| | Median = middle value of a list of data sorted from least to greatest. | If there is an even number of values, the median will be the average of the middle two values. |
| | Mode = most common value. | Least affected by outliers. |
| **Measures of dispersion** | Standard deviation = how much variability exists in a set of values, around the mean of these values.<br>Standard error = an estimate of how much variability exists in a (theoretical) set of sample means around the true population mean. | $\sigma$ = SD; n = sample size.<br>Variance = $(SD)^2$.<br>SE = $\sigma/\sqrt{n}$.<br>SE ↓ as n ↑. |
| **Normal distribution** | Gaussian, also called bell-shaped.<br>Mean = median = mode.<br>For normal distribution, mean is the best measure of central tendency. |  |

## Nonnormal distributions

| | | |
|---|---|---|
| Bimodal | Suggests two different populations (eg, metabolic polymorphism such as fast vs slow acetylators; age at onset of Hodgkin lymphoma; suicide rate by age). |  |
| Positive skew | Typically, mean > median > mode.<br>Asymmetry with longer tail on right. |  |
| Negative skew | Typically, mean < median < mode.<br>Asymmetry with longer tail on left. |  |

## Statistical hypothesis testing

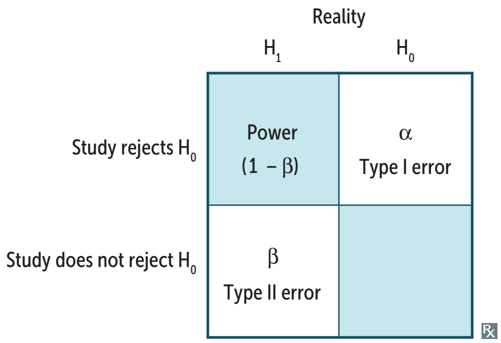
| | |
|---|---|
| **Null hypothesis ($H_0$)** | Hypothesis of no difference or relationship (eg, there is no association between the disease and the risk factor in the population). |
| **Alternative hypothesis ($H_1$)** | Hypothesis of some difference or relationship (eg, there is some association between the disease and the risk factor in the population). |
| ***p*-value** | The probability of obtaining test results at least as extreme as those observed during the test, assuming that $H_0$ is correct. |

## Outcomes of statistical hypothesis testing

**Correct result**

Stating that there is an effect or difference when one exists ($H_0$ rejected in favor of $H_1$).

Stating that there is no effect or difference when none exists ($H_0$ not rejected).




Blue shading = correct result.

### Testing errors

**Type I error ($\alpha$)**

Stating that there is an effect or difference when none exists ($H_0$ incorrectly rejected in favor of $H_1$).

$\alpha$ is the probability of making a type I error (usually 0.05 is chosen). If $p < \alpha$, then assuming $H_0$ is true, the probability of obtaining the test results would be less than the probability of making a type I error. $H_0$ is therefore rejected as false.

Statistical significance ≠ clinical significance.

Also called false-positive error.

1st time boy cries wolf, the town believes there is a wolf, but there is not (false positive).

You can never "prove" $H_1$, but you can reject the $H_0$ as being very unlikely.

**Type II error ($\beta$)**

Stating that there is not an effect or difference when one exists ($H_0$ is not rejected when it is in fact false).

$\beta$ is the probability of making a type II error. $\beta$ is related to statistical power $(1 - \beta)$, which is the probability of rejecting $H_0$ when it is false.

↑ power and ↓ $\beta$ by:

- ↑ sample size
- ↑ expected effect size
- ↑ precision of measurement

Also called false-negative error.

2nd time boy cries wolf, the town believes there is no wolf, but there is one.

If you ↑ sample size, you ↑ power. There is **power in numbers**.

**Confidence interval**

Range of values within which the true mean of the population is expected to fall, with a specified probability.

CI = 1 – $\alpha$. The 95% CI (corresponding to $\alpha$ = 0.05) is often used. As sample size increases, CI narrows.

CI for sample mean = $\bar{x} \pm Z(SE)$

For the 95% CI, Z = 1.96.

For the 99% CI, Z = 2.58.

$H_0$ is rejected (and results are significant) when:

- 95% CI for mean difference excludes 0
- 95% CI OR or RR excludes 1
- CIs between two groups do not overlap

$H_0$ is accepted (and results are significant) when:.

- 95% CI for mean difference includes 0
- 95% CI OR or RR includes 1
- CIs between two groups do overlap

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**Meta-analysis**

A method of statistical analysis that pools summary data (eg, means, RRs) from multiple studies for a more precise estimate of the size of an effect. Also estimates heterogeneity of effect sizes between studies.

Improves power, strength of evidence, and generalizability (external validity) of study findings. Limited by quality of individual studies and bias in study selection.

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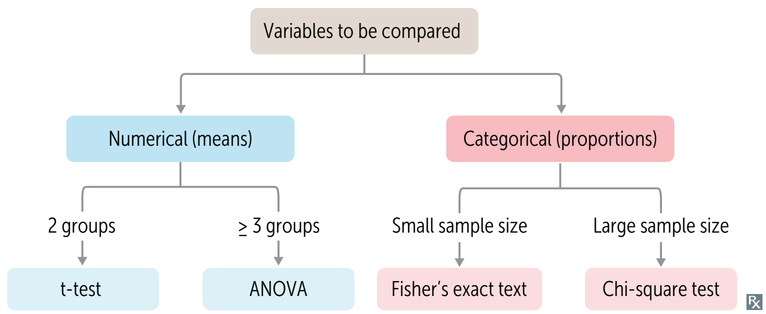
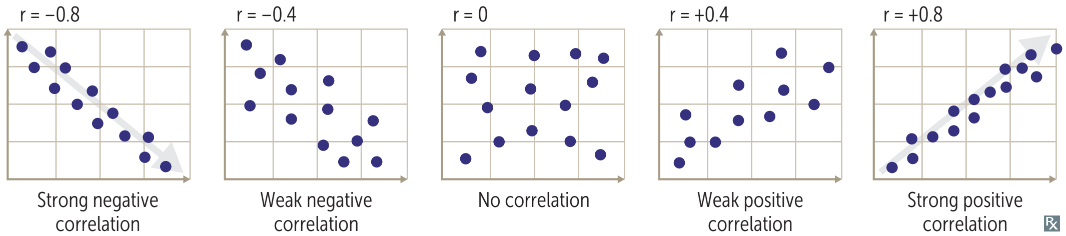
**Common statistical tests**

| | | |
|---|---|---|
| *t*-test | Checks differences between **means** of **2** groups. | **T**ea is **mean**t for **2**.<br>Example: comparing the mean blood pressure between men and women. |
| ANOVA | Checks differences between means of **3** or more groups. | **3** words: **AN**alysis **O**f **VA**riance.<br>Example: comparing the mean blood pressure between members of 3 different ethnic groups. |
| Fisher's exact test | Checks differences between 2 percentages or proportions of categorical, nominal outcomes. Use instead of chi-square test with small populations. | Example: comparing the percentage of 20 men and 20 women with hypertension. |
| Chi-square ($\chi^2$) | Checks differences between 2 or more percentages or proportions of **categorical** outcomes (not mean values). | Pronounce **chi-tegorical**.<br>Example: comparing the proportion of members of 3 age groups who have essential hypertension. |



| | |
|---|---|
| **Pearson correlation coefficient** | A measure of the linear correlation between two variables. *r* is always between −1 and +1. The closer the absolute value of *r* is to 1, the stronger the linear correlation between the 2 variables. Variance is how much the measured values differ from the average value in a data set.<br>Positive *r* value → positive correlation (as one variable ↑, the other variable ↑).<br>Negative *r* value → negative correlation (as one variable ↑, the other variable ↓).<br>Coefficient of determination = $r^2$ (amount of variance in one variable that can be explained by variance in another variable). |




## ▶ PUBLIC HEALTH SCIENCES—ETHICS

### Core ethical principles

| | |
|---|---|
| **Autonomy** | Obligation to respect patients as individuals (truth-telling, confidentiality), to create conditions necessary for autonomous choice (informed consent), and to honor their preference in accepting or not accepting medical care. |
| **Beneficence** | Physicians have a special ethical (fiduciary) duty to act in the patient's best interest. May conflict with autonomy (an informed patient has the right to decide) or what is best for society (eg, mandatory TB treatment). Traditionally, patient interest supersedes. |
| **Nonmaleficence** | "Do no harm." Must be balanced against beneficence; if the benefits outweigh the risks, a patient may make an informed decision to proceed (most surgeries and medications fall into this category). |
| **Justice** | To treat persons fairly and equitably. This does not always imply equally (eg, triage). |

**Decision-making capacity**

Physician must determine whether the patient is psychologically and legally capable of making a particular healthcare decision. Note that decisions made with capacity cannot be revoked simply if the patient later loses capacity. Intellectual disabilities and mental illnesses are not exclusion criteria for informed decision-making unless their condition presently impairs their ability to make healthcare decisions.

Capacity is determined by a physician for a specific healthcare-related decision (eg, to refuse medical care). Competency is determined by a judge and usually refers to more global categories of decision making (eg, legally unable to make any healthcare-related decision).

Components (assessing capacity is of **MASSIVE** importance):

- Decision is not a result of **M**ental illness exacerbation
- Patient is ≥ 18 years of **A**ge or otherwise legally emancipated
- Decision is not a result of altered mental **S**tatus (eg, delirium, intoxication)
- Decision remains **S**table over time
- Patient is **I**nformed and understands
- Decision is consistent with patient's **V**alues and goals
- Patient **E**xpresses preferences

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**Informed consent**

A process (not just a document/signature) that requires:

- Disclosure: discussion of pertinent information (using medical interpreter, if needed)
- Understanding: ability to comprehend
- Capacity: ability to reason and make one's own decisions (distinct from competence, a legal determination)
- Voluntariness: freedom from coercion and manipulation

Patients must have a comprehensive understanding of their diagnosis and the risks/benefits of proposed treatment and alternative options, including no treatment.

Patient must be informed of their right to revoke written consent at any time, even orally.

Exceptions to informed consent (**WIPE** it away):

- **W**aiver—patient explicitly relinquishes the right of informed consent
- Legally **I**ncompetent—patient lacks decision-making capacity (obtain consent from legal surrogate)
- Therapeutic **P**rivilege—withholding information when disclosure would severely harm the patient or undermine informed decision-making capacity
- **E**mergency situation—implied consent may apply

| | | |
|---|---|---|
| **Consent for minors** | A minor is generally any person < 18 years old. Parental consent laws in relation to healthcare vary by state. In general, parental consent should be obtained, but exceptions exist for emergency treatment (eg, blood transfusions) or if minor is legally emancipated (eg, married, self-supporting, or in the military). | Situations in which parental consent is usually not required:<br>▪ **Sex** (contraception, STIs, prenatal care—usually not abortion)<br>▪ **Drugs** (substance use disorder treatment)<br>▪ **Rock and roll** (emergency/trauma)<br>Physicians should always encourage healthy minor-guardian communication.<br>Physician should seek a minor's assent (agreement of someone unable to legally consent) even if their consent is not required. |

| | |
|---|---|
| **Advance directives** | Instructions given by a patient in anticipation of the need for a medical decision. Details vary per state law. |
| **Oral advance directive** | Incapacitated patient's prior oral statements commonly used as guide. Problems arise from variance in interpretation. If patient was informed, directive was specific, patient made a choice, and decision was repeated over time to multiple people, then the oral directive is more valid. |
| **Written advance directive** | Delineates specific healthcare interventions that patient anticipates accepting or rejecting during treatment for a critical or life-threatening illness. A living will is an example. |
| **Medical power of attorney** | Patient designates an agent to make medical decisions in the event that the patient loses decision-making capacity. Patient may also specify decisions in clinical situations. Can be revoked by patient if decision-making capacity is intact. More flexible than a living will. |
| **Do not resuscitate order** | DNR order prohibits cardiopulmonary resuscitation (CPR). Patient may still consider other life-sustaining measures (eg, intubation, feeding tube, chemotherapy). |

| | |
|---|---|
| **Surrogate decision-maker** | If a patient loses decision-making capacity and has not prepared an advance directive, individuals (surrogates) who know the patient must determine what the patient would have done. Priority of surrogates: **spouse** → adult **chi**ldren → **p**arents → **s**iblings → other relatives (the **spouse ChiPS** in). |

| | |
|---|---|
| **Confidentiality** | Confidentiality respects patient privacy and autonomy. If the patient is incapacitated or the situation is emergent, disclosing information to family and friends should be guided by professional judgment of patient's best interest. The patient may voluntarily waive the right to confidentiality (eg, insurance company request).<br>General principles for exceptions to confidentiality:<br>▪ Potential physical harm to self or others is serious and imminent<br>▪ Alternative means to warn or protect those at risk is not possible<br>▪ Steps can be taken to prevent harm<br>Examples of exceptions to patient confidentiality (many are state specific) include the following ("The physician's good judgment **SAVED** the day"):<br>▪ Patients with **S**uicidal/homicidal ideation<br>▪ **A**buse (children, elderly, and/or prisoners)<br>▪ Duty to protect—state-specific laws that sometimes allow physician to inform or somehow protect potential **V**ictim from harm<br>▪ Patients with **E**pilepsy and other impaired automobile drivers<br>▪ Reportable **D**iseases (eg, STIs, hepatitis, food poisoning); physicians may have a duty to warn public officials, who will then notify people at risk. Dangerous communicable diseases, such as TB or Ebola, may require involuntary treatment. |

## ▸ PUBLIC HEALTH SCIENCES—COMMUNICATION SKILLS

### Patient-centered interviewing techniques

| | |
|---|---|
| **Introduction** | Introduce yourself and address the patient by preferred name. Sit at eye-level near the patient. |
| **Agenda setting** | Identify concerns and set goals by developing joint agenda between the physician and the patient. |
| **Reflection** | Actively listen and synthesize information offered by the patient, particularly with respect to primary concern(s). |
| **Validation** | Legitimize or affirm the patient's perspectives. |
| **Recapitulation** | Summarize what the patient has said so far to ensure correct interpretation. |
| **Facilitation** | Encourage the patient to speak freely without guiding responses or leading questions. Allow the patient to ask questions throughout the encounter. |

| Expressing empathy | PEARLS |
|---|---|
| Partnership | Reassure the patient that you will work together through difficult times, and offer appropriate resources. |
| Empathy | Acknowledge the emotions displayed and demonstrate understanding of why the patient is feeling that way. |
| Apology | Take personal responsibility when appropriate, or offer condolences for the patient's situation. |
| Respect | Commend the patient for coming in to discuss a problem, pushing through challenging circumstances, keeping a positive attitude, or other constructive behaviors. |
| Legitimization | Assure the patient that emotional responses are understandable or common. |
| Support | Offer to help the patient through difficult times. |

| Delivering bad news | SPIKES |
|---|---|
| Setting | Offer in advance for the patient to bring support. Eliminate distractions, ensure privacy, and sit down with the patient to talk. |
| Perception | Determine the patient's understanding and expectations of the situation. |
| Invitation | Obtain the patient's permission to disclose the news and what level of detail is desired. |
| Knowledge | Share the information in small pieces without medical jargon, allowing time to process. Assess the patient's understanding. |
| Emotions | Acknowledge the patient's emotions, and provide opportunity to express them. Listen and offer empathetic responses. |
| Strategy | If the patient feels ready, discuss treatment options and goals of care. Offer an agenda for the next appointment. |

**Gender- and sexuality-inclusive history taking**

Avoid making assumptions about sexual orientation, gender identity, gender expression, and behavior (eg, a patient who identifies as heterosexual may engage in same-sex sexual activity).

Use gender-neutral terms (eg, refer to a patient's "partner" rather than assuming a spouse's gender).

A patient's sex assigned at birth and gender identity may differ.

Consider stating what pronouns you use when you introduce yourself (eg, "I'm Dr. Smith, and I use she/her pronouns") and asking patients how they would like to be addressed.

Reassure them about the confidentiality of their appointments and be sensitive to the fact that patients may not be open about their sexual orientation or gender identity to others in their life.

Do not bring up gender or sexuality if it is not relevant to the visit (eg, a gender-nonconforming patient seeking care for a hand laceration).

**Trauma-informed communication**

Patients with a history of a traumatic experience should receive thorough behavioral health screenings. Regularly assess mood, substance use, social supports, and suicide risk.

Focus assessments on trauma-related symptoms that interfere with social and occupational function.

Do not ask invasive questions requiring the patient to describe trauma in detail.

Before the physical exam, reassure patients that they may signal to end it immediately if they experience too much physical or emotional discomfort. Offer the presence of additional staff for support.

| | |
|---|---|
| **Motivational interviewing** | Counseling technique to facilitate behavior modification by helping patients resolve ambivalence about change. Useful for many conditions (eg, nicotine dependence, obesity). Helpful when patient has some desire to change, but it does not require that the patient be committed to making the change. May involve asking patients to examine how their behavior interferes with their life or why they might want to change it. Assess barriers (eg, food access, untreated trauma) that may make behavior change difficult.<br>Assessing a patient's readiness for change is also important for guiding physician-suggested goals. These goals should be **S**pecific, **M**easurable, **A**chievable, **R**elevant, and **T**ime bound (**SMART**). |
| **Communicating with patients with disabilities** | Use "person-first" language, which refers to "a person with a disability" rather than "a disabled person." Consider asking patients what terms they use to describe themselves.<br>Under most circumstances, talk directly to the patient. Do not assume that nonverbal patients do not understand. Accompanying caregivers can add information to any discussion as needed.<br>Ask if assistance is desired rather than assuming the patient cannot do something alone. Most people, including people with disabilities, value their independence.<br>For patients with speech difficulties, provide extra time for the interview. If their speech is difficult to understand, consider asking them to write down a few words or ask them to rephrase their sentence. Repeat what they said to ensure you understood it correctly.<br>For patients with a cognitive impairment, use concrete, specific language. Ask simple, direct questions. Eliminate background noise and distractions. Do not assume the patient can read. Adjust to how the patient understands best (eg, use hand gestures or ask them to demonstrate a task).<br>Ask patients who are deaf or hard of hearing their preferred mode of communication. Use light touch or waving to get their attention. For patients who prefer to speak and lipread, eliminate background noise, face the patient, and do not change your mode of speaking.<br>As with other parts of a medical history, do not bring up a disability if it is not relevant to a visit (eg, a patient in a wheelchair with an ear infection). Do not skip relevant parts of the physical exam even if the disability makes the exam challenging. |
| **Use of interpreters** | Visits with a patient who speaks little English should utilize a professionally trained medical interpreter unless the physician is also fluent in the patient's preferred language. Interpretation services may be provided in person, by telephone, or by video call. If the patient prefers to utilize a family member, this should be recorded in the chart.<br>Do not assume that a patient is a poor English speaker because of name, skin tone, or accent. Ask the patient what language is preferred.<br>The physician should make eye contact with the patient and speak to them normally, without use of third-person statements such as "tell him."<br>Allow extra time for the interview, and ask one question at a time.<br>For in-person spoken language interpretation, the interpreter should ideally be next to or slightly behind the patient. For sign language interpretation, the interpreter should be next to or slightly behind the physician. |

**Challenging patient and ethical scenarios**

The most appropriate response is usually one that is open ended, empathetic, and patient centered. It often honors one or more of the principles of autonomy, beneficence, nonmaleficence, and justice. Appropriate responses are respectful of patients and other members of the healthcare team.

| SITUATION | APPROPRIATE RESPONSE |
| --- | --- |
| Patient is not adherent. | Determine whether there are financial, logistical, or other obstacles preventing the patient's adherence. Do not coerce the patient into adhering or refer the patient to another physician. |
| Patient desires an unnecessary procedure. | Attempt to understand why the patient wants the procedure and address underlying concerns. Do not refuse to see the patient or refer to another physician. Avoid performing unnecessary procedures. |
| Patient has difficulty taking medications. | Determine what factors are involved in the patient's difficulties. If comprehension or memory are issues, use techniques such as providing written instructions, using the teach-back method, or simplifying treatment regimens. |
| Family members ask for information about patient's prognosis. | Avoid discussing issues with relatives without the patient's permission. |
| A patient's family member asks you not to disclose the results of a test if the prognosis is poor because the patient will be "unable to handle it." | Explore why the family member believes this would be detrimental, including possible cultural factors. Explain that if the patient would like to know information concerning care, it will not be withheld. However, if you believe the patient might seriously harm self or others if informed, you may invoke therapeutic privilege and withhold the information. |
| A 17-year-old is pregnant and requests an abortion. | Many states require parental notification or consent for minors for an abortion. Unless there are specific medical risks associated with pregnancy, a physician should not sway the patient's decision for, or against, an elective abortion (regardless of patient's age or fetal condition). Discuss options for terminating the pregnancy and refer to abortion care, if needed. |
| A 15-year-old is pregnant and wants to raise the child. Her parents want you to tell her to give the child up for adoption. | The patient retains the right to make decisions regarding her child, even if her parents disagree. Provide information to the teenager about the practical aspects of caring for a baby. Discuss options for terminating the pregnancy, if requested. Encourage discussion between the teenager and her parents to reach the best decision. |
| A terminally ill patient requests physician-assisted dying. | The overwhelming majority of states prohibit most forms of physician-assisted dying. Physicians may, however, prescribe medically appropriate analgesics even if they potentially shorten the patient's life. |
| Patient is suicidal. | Assess the seriousness of the threat. If patient is actively suicidal with a plan, suggest remaining in the hospital voluntarily; patient may be hospitalized involuntarily if needed. |
| Patient states that you are attractive and asks if you would go on a date. | Use a chaperone if necessary. Romantic relationships with patients are never appropriate. It may be necessary to transition care to another physician. |
| A woman who had a mastectomy says she now feels "ugly." | Find out why the patient feels this way. Do not offer falsely reassuring statements (eg, "You still look good"). |
| Patient is angry about the long time spent in the waiting room. | Acknowledge the patient's anger, but do not take a patient's anger personally. Thank the patient for being patient and apologize for any inconvenience. Stay away from efforts to explain the delay. |
| Patient is upset with treatment received from another physician. | Suggest that the patient speak directly to that physician regarding the concern. If the problem is with a member of the office staff, tell the patient you will speak to that person. |
| An invasive test is performed on the wrong patient. | Regardless of the outcome, a physician is ethically obligated to inform a patient that a mistake has been made. |

### Challenging patient and ethical scenarios *(continued)*

| SITUATION | APPROPRIATE RESPONSE |
| --- | --- |
| A patient requires a treatment not covered by insurance. | Discuss all treatment options with patients, even if some are not covered by their insurance companies. Inform patient of financial assistance programs. |
| A 7-year-old boy loses a sister to cancer and now feels responsible. | At ages 5–7, children begin to understand that death is permanent, that all life functions end completely at death, and that everything that is alive eventually dies. Provide a direct, concrete description of his sister's death. Avoid clichés and euphemisms. Reassure the boy that he is not responsible. Identify and normalize fears and feelings. Encourage play and healthy coping behaviors (eg, remembering her in his own way). |
| Patient is victim of intimate partner violence. | Ask if patient is safe and help devise an emergency plan if there isn't one. Educate patient on intimate partner violence resources. Do not necessarily pressure patient to leave a partner or disclose the incident to the authorities (unless required by state law). |
| Patient wants to try alternative or holistic medicine. | Explore any underlying reasons with the patient in a supportive, nonjudgmental manner. Advise the patient of known benefits and risks of treatment, including adverse effects, contraindications, and medication interactions. |
| Physician colleague presents to work impaired. | This presents a potential risk to patient safety. You have an ethical and usually a legal obligation to report impaired colleagues so they can cease patient care and receive appropriate assistance in a timely manner. Seek guidance in reporting as procedures and applicable law vary by institution and state. |
| Patient is officially determined to suffer brain death. Patient's family insists on maintaining life support indefinitely because patient is still moving when touched. | Gently explain to family that there is no chance of recovery, and that brain death is equivalent to death. Movement is due to spinal arc reflex and is not voluntary. Bring case to appropriate ethics board regarding futility of care and withdrawal of life support. |
| A pharmaceutical company offers you a sponsorship in exchange for advertising its new drug. | Reject this offer. Generally, decline gifts and sponsorships to avoid any conflict of interest. The AMA Code of Ethics does make exceptions for gifts directly benefitting patients; special funding for medical education of students, residents, fellows; grants whose recipients are chosen by independent institutional criteria; and funds that are distributed without attribution to sponsors. |
| Patient requests a nonemergent procedure that is against your personal or religious beliefs. | Provide accurate and unbiased information so patients can make an informed decision. In a neutral, nonjudgmental manner, explain to the patient that you do not perform the procedure but offer to refer to another physician. |
| Mother and 15-year-old daughter are unresponsive following a car accident and are bleeding internally. Father says do not transfuse because they are Jehovah's Witnesses. | Transfuse daughter, but do not transfuse mother. Emergent care can be refused by the healthcare proxy for an adult, particularly when patient preferences are known or reasonably inferred, but not for a minor based solely on faith. |
| A dependent patient presents with injuries inconsistent with caretaker's story. | Document detailed history and physical. If possible and appropriate, interview the patient alone. Provide any necessary medical care. If suspicion remains, contact the appropriate agencies or authorities (eg, child or adult protective services) for an evaluation. Inform the caretaker of your obligation to report. Physicians are required by law to report any reasonable suspicion of abuse, neglect, or endangerment. |
| A pediatrician recommends standard vaccinations for a patient, but the child's parent refuses. | Address any concerns the parent has. Explain the risks and benefits of vaccinations and why they are recommended. Do not administer routine vaccinations without the parent's consent. |

## ▶ PUBLIC HEALTH SCIENCES—HEALTHCARE DELIVERY

### Disease prevention

| | |
|---|---|
| **Primary disease prevention** | Prevent disease before it occurs (eg, HPV vaccination) |
| **Secondary disease prevention** | Screen early for and manage existing but asymptomatic disease (eg, Pap smear for cervical cancer) |
| **Tertiary disease prevention** | Treatment to reduce complications from disease that is ongoing or has long-term effects (eg, chemotherapy) |
| **Quaternary disease prevention** | Quit (avoid) unnecessary medical interventions to minimize incidental harm (eg, imaging studies, optimizing medications to reduce polypharmacy) |

### Major medical insurance plans

| PLAN | PROVIDERS | PAYMENTS | SPECIALIST CARE |
|---|---|---|---|
| **Exclusive provider organization** | Restricted to limited panel (except emergencies) | | No referral required |
| **Health maintenance organization** | Restricted to limited panel (except emergencies) | Most affordable | Requires referral from primary care provider |
| **Point of service** | Patient can see providers outside network | Higher copays and deductibles for out-of-network services | Requires referral from primary care provider |
| **Preferred provider organization** | Patient can see providers outside network | Higher copays and deductibles for all services | No referral required |
| **Accountable care organization** | Providers voluntarily enroll | Medicare | Specialists voluntarily enroll |

### Healthcare payment models

| | |
|---|---|
| **Bundled payment** | Healthcare organization receives a set amount per service, regardless of ultimate cost, to be divided among all providers and facilities involved. |
| **Capitation** | Physicians receive a set amount per patient assigned to them per period of time, regardless of how much the patient uses the healthcare system. Used by some HMOs. |
| **Discounted fee-for-service** | Insurer and/or patient pays for each individual service at a discounted rate predetermined by providers and payers (eg, PPOs). |
| **Fee-for-service** | Insurer and/or patient pays for each individual service. |
| **Global payment** | Insurer and/or patient pays for all expenses associated with a single incident of care with a single payment. Most commonly used during elective surgeries, as it covers the cost of surgery as well as the necessary pre- and postoperative visits. |

| | | |
|---|---|---|
| **Medicare and Medicaid** | Medicare and Medicaid—federal social healthcare programs that originated from amendments to the Social Security Act.<br>Medicare is available to patients ≥ 65 years old, < 65 with certain disabilities, and those with end-stage renal disease.<br>Medicaid is joint federal and state health assistance for people with limited income and/or resources. | MedicarE is for Elderly.<br>MedicaiD is for Disadvantaged.<br><br>The 4 parts of Medicare:<br>▪ Part A: hospital Admissions, including hospice, skilled nursing<br>▪ Part B: Basic medical bills (eg, physician fees, diagnostic testing)<br>▪ Part C: (parts A + B = Combo) delivered by approved private companies<br>▪ Part D: prescription Drugs |
| **Hospice care** | Medical care focused on providing comfort and palliation instead of definitive cure. Available to patients on Medicare or Medicaid and in most private insurance plans whose life expectancy is < 6 months.<br>During end-of-life care, priority is given to improving the patient's comfort and relieving pain (often includes opioid, sedative, or anxiolytic medications). Facilitating comfort is prioritized over potential side effects (eg, respiratory depression). This prioritization of positive effects over negative effects is called the principle of double effect. | |

**Common causes of death (US) by age**

| | < 1 YR | 1–14 YR | 15–34 YR | 35–44 YR | 45–64 YR | 65+ YR |
|---|---|---|---|---|---|---|
| #1 | Congenital malformations | Unintentional injury | Unintentional injury | Unintentional injury | Cancer | Heart disease |
| #2 | Preterm birth | Cancer | Suicide | Cancer | Heart disease | Cancer |
| #3 | Pregnancy complications | Congenital malformations | Homicide | Heart disease | Unintentional injury | Chronic respiratory disease |

## ▶ PUBLIC HEALTH SCIENCES—QUALITY AND SAFETY

**Safety culture**

Organizational environment in which everyone can freely bring up safety concerns without fear of penalty. Facilitates error identification.

Event reporting systems collect data on errors for internal and external monitoring.

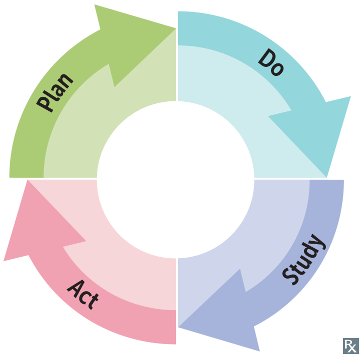
**Human factors design**

Forcing functions (those that prevent undesirable actions [eg, connecting feeding syringe to IV tubing]) are the most effective.
Standardization improves process reliability (eg, clinical pathways, guidelines, checklists).
Simplification reduces wasteful activities (eg, consolidating electronic medical records).

Deficient designs hinder workflow and lead to staff workarounds that bypass safety features (eg, patient ID barcodes affixed to computers due to unreadable wristbands).

**PDSA cycle**

Process improvement model to test changes in real clinical setting. Impact on patients:
- Plan—define problem and solution
- Do—test new process
- Study—measure and analyze data
- Act—integrate new process into workflow

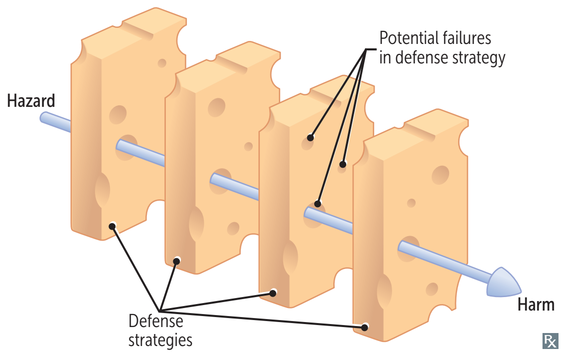



**Quality measurements**

| | MEASURE | EXAMPLE |
|---|---|---|
| Structural | Physical equipment, resources, facilities | Number of diabetes educators |
| Process | Performance of system as planned | Percentage of patients with diabetes whose $HbA_{1c}$ was measured in the past 6 months |
| Outcome | Impact on patients | Average $HbA_{1c}$ of patients with diabetes |
| Balancing | Impact on other systems/outcomes | Incidence of hypoglycemia among patients who tried an intervention to lower $HbA_{1c}$ |

**Swiss cheese model**

Focuses on systems and conditions rather than an individual's error. The risk of a threat becoming a reality is mitigated by differing layers and types of defenses. Patient harm can occur despite multiple safeguards when "the holes in the cheese line up."



| | | |
|---|---|---|
| **Types of medical errors** | May involve patient identification, diagnosis, monitoring, nosocomial infection, medications, procedures, devices, documentation, handoffs. Medical errors should be disclosed to patients, independent of immediate outcome (harmful or not). | |
| **Active error** | Occurs at level of frontline operator (eg, wrong IV pump dose programmed). | Immediate impact. |
| **Latent error** | Occurs in processes indirect from operator but impacts patient care (eg, different types of IV pumps used within same hospital). | Accident waiting to happen. |
| **Never event** | Adverse event that is identifiable, serious, and usually preventable (eg, scalpel retained in a surgical patient's abdomen). | Major error that should never occur. |
| **Near miss** | Unplanned event that does not result in harm but has the potential to do so (eg, pharmacist recognizes a medication interaction and cancels the order). | Narrow prevention of harm that exposes dangers. |

## Burnout vs fatigue

| | |
|---|---|
| **Burnout** | Prolonged, excessive stress → cynicism, detachment, ↓ motivation and interest, sense of failure and helplessness, ↓ immunity. Medical errors due to reduced professional efficacy. |
| **Fatigue** | Sleep deprivation → ↓ energy and motivation, cognitive impairment. Medical errors due to compromised intellectual function. |

## Medical error analysis

| | DESIGN | METHODS |
|---|---|---|
| **Root cause analysis** | Retrospective approach. Applied after failure event to prevent recurrence. | Uses records and participant interviews to identify all the underlying problems (eg, process, people, environment, equipment, materials, management) that led to an error. |
| **Failure mode and effects analysis** | Forward-looking approach. Applied before process implementation to prevent failure occurrence. | Uses inductive reasoning to identify all the ways a process might fail and prioritizes them by their probability of occurrence and impact on patients. |

## NOTES

SECTION III

# High-Yield Organ Systems

*"Symptoms, then, are in reality nothing but the cry from suffering organs."*

—Jean-Martin Charcot

*"Man is an intelligence in servitude to his organs."*

—Aldous Huxley

*"When every part of the machine is correctly adjusted and in perfect harmony, health will hold dominion over the human organism by laws as natural and immutable as the laws of gravity."*

—Andrew T. Still

## ▸ APPROACHING THE ORGAN SYSTEMS

In this section, we have divided the High-Yield Facts into the major **Organ Systems.** Within each Organ System are several subsections, including **Embryology, Anatomy, Physiology, Pathology,** and **Pharmacology.** As you progress through each Organ System, refer back to information in the previous subsections to organize these basic science subsections into a "vertically integrated" framework for learning. Below is some general advice for studying the organ systems by these subsections.

### Embryology

Relevant embryology is included in each organ system subsection. Embryology tends to correspond well with the relevant anatomy, especially with regard to congenital malformations.

### Anatomy

Several topics fall under this heading, including gross anatomy, histology, and neuroanatomy. Do not memorize all the small details; however, do not ignore anatomy altogether. Review what you have already learned and what you wish you had learned. Many questions require two or more steps. The first step is to identify a structure on anatomic cross section, electron micrograph, or photomicrograph. The second step may require an understanding of the clinical significance of the structure.

While studying, emphasize clinically important material. For example, be familiar with gross anatomy and radiologic anatomy related to specific diseases (eg, Pancoast tumor, Horner syndrome), traumatic injuries (eg, fractures, sensory and motor nerve deficits), procedures (eg, lumbar puncture), and common surgeries (eg, cholecystectomy). There are also many questions on the exam involving x-rays, CT scans, and neuro MRI scans. Many students suggest browsing through a general radiology atlas, pathology atlas, and histology atlas. Focus on learning basic anatomy at key levels in the body (eg, sagittal brain MRI; axial CT of the midthorax, abdomen, and pelvis). Basic neuroanatomy (especially pathways, blood supply, and functional anatomy), associated neuropathology, and neurophysiology have good yield. Please note that many of the photographic images in this book are for illustrative purposes and are not necessarily reflective of Step 1 emphasis.

### Physiology

The portion of the examination dealing with physiology is broad and concept oriented and thus does not lend itself as well to fact-based review. Diagrams are often the best study aids, especially given the increasing number of questions requiring the interpretation of diagrams. Learn to apply basic physiologic relationships in a variety of ways (eg, the Fick equation, clearance equations). You are seldom asked to perform complex calculations. Hormones

are the focus of many questions; learn where and how they are synthesized, their regulatory mechanisms and sites of action.

A large portion of the physiology tested on the USMLE Step 1 is clinically relevant and involves understanding physiologic changes associated with pathologic processes (eg, changes in pulmonary function with COPD). Thus, it is worthwhile to review the physiologic changes that are found with common pathologies of the major organ systems (eg, heart, lungs, kidneys, GI tract) and endocrine glands.

### Pathology

Questions dealing with this discipline are difficult to prepare for because of the sheer volume of material involved. Review the basic principles and hallmark characteristics of the key diseases. Given the clinical orientation of Step 1, it is no longer sufficient to know only the "buzzword" associations of certain diseases (eg, café-au-lait macules and neurofibromatosis); you must also recognize the clinical descriptions of these high-yield physical exam findings.

Given the clinical slant of the USMLE Step 1, it is also important to review the classic presenting signs and symptoms of diseases as well as their associated laboratory findings. Delve into the signs, symptoms, and pathophysiology of major diseases that have a high prevalence in the United States (eg, alcohol use disorder, diabetes, hypertension, heart failure, ischemic heart disease, infectious disease). Be prepared to think one step beyond the simple diagnosis to treatment or complications.

The examination includes a number of color photomicrographs and photographs of gross specimens that are presented in the setting of a brief clinical history. However, read the question and the choices carefully before looking at the illustration, because the history will help you identify the pathologic process. Flip through an illustrated pathology textbook, color atlases, and appropriate Web sites in order to look at the pictures in the days before the exam. Pay attention to potential clues such as age, sex, ethnicity, occupation, recent activities and exposures, and specialized lab tests.

### Pharmacology

Preparation for questions on pharmacology is straightforward. Learning all the key drugs and their characteristics (eg, mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the "classic" and distinguishing toxicities of the major drugs. Do not bother with drug dosages or brand names. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.

NOTES

# Cardiovascular

*"As for me, except for an occasional heart attack, I feel as young as I ever did."*

—Robert Benchley

*"Hearts will never be practical until they are made unbreakable."*

—*The Wizard of Oz*

*"As the arteries grow hard, the heart grows soft."*

—H. L. Mencken

*"Nobody has ever measured, not even poets, how much the heart can hold."*

—Zelda Fitzgerald

*"The art of medicine has its roots in the heart."*

—Paracelsus

*"It is not the size of the man but the size of his heart that matters."*

—Evander Holyfield

The cardiovascular system is one of the highest yield areas for the boards and, for some students, may be the most challenging. Focusing on understanding the mechanisms instead of memorizing the details can make a big difference, especially for this topic. Pathophysiology of atherosclerosis and heart failure, MOA of drugs (particular physiology interactions) and their adverse effects, ECGs of heart blocks, the cardiac cycle, and the Starling curve are some of the more high-yield topics. Differentiating between systolic and diastolic dysfunction is also very important. Heart murmurs and maneuvers that affect these murmurs have also been high yield and may be asked in a multimedia format.

## ▸ CARDIOVASCULAR—EMBRYOLOGY

### Heart morphogenesis

First functional organ in vertebrate embryos; beats spontaneously by week 4 of development.

#### Cardiac looping

Primary heart tube loops to establish left-right polarity; begins in week 4 of development.

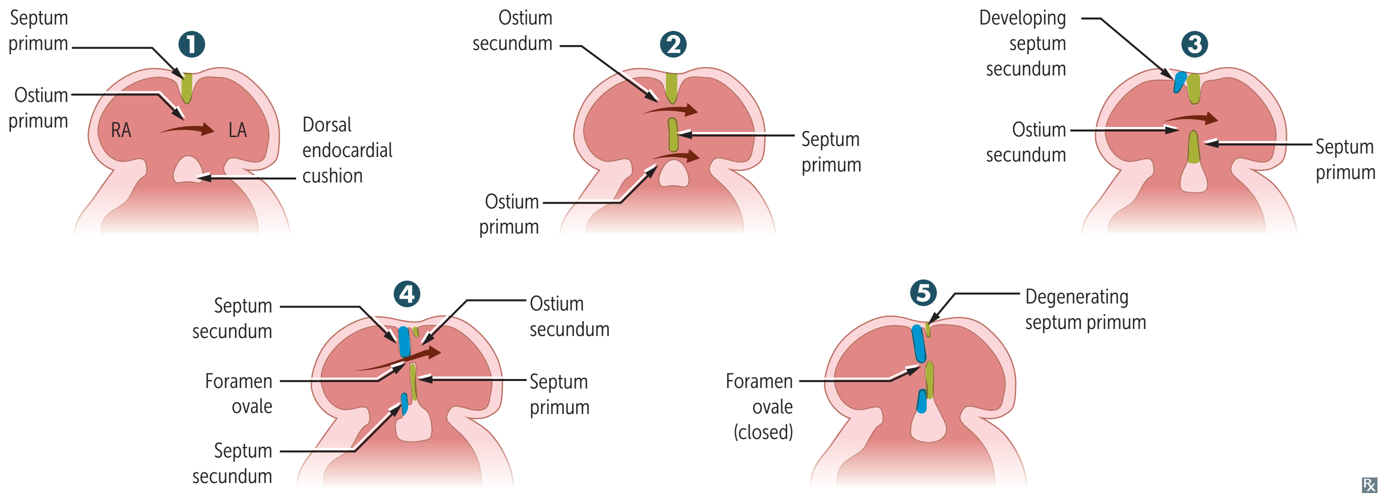
Defect in left-right dynein (involved in left-right asymmetry) can lead to dextrocardia, as seen in Kartagener syndrome.

#### Septation of the chambers

##### Atria

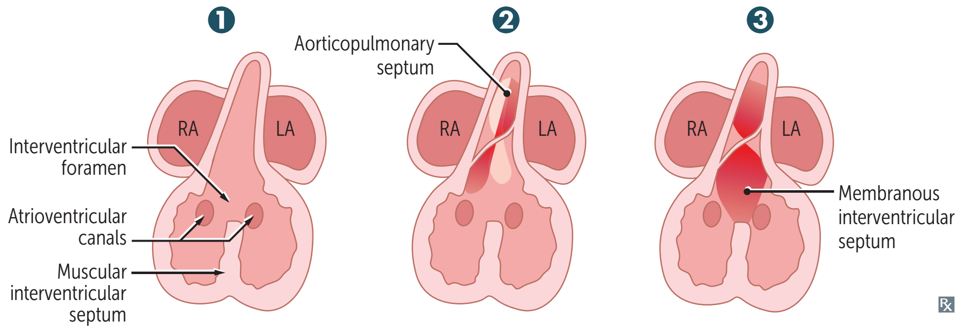
1. Septum primum grows toward endocardial cushions, narrowing ostium primum.
2. Ostium secundum forms in septum primum due to cell death (ostium primum regresses).
3. Septum secundum develops on the right side of septum primum, as ostium secundum maintains right-to-left shunt.
4. Septum secundum expands and covers most of ostium secundum. The residual foramen is the foramen ovale.
5. Remaining portion of septum primum forms the one-way valve of the foramen ovale.
6. Septum primum closes against septum secundum, sealing the foramen ovale soon after birth because of ↑ LA pressure and ↓ RA pressure.
7. Septum secundum and septum primum fuse during infancy/early childhood, forming the atrial septum.

Patent foramen ovale—caused by failure of septum primum and septum secundum to fuse after birth; most are left untreated. Can lead to paradoxical emboli (venous thromboemboli entering the systemic arterial circulation through right-to-left shunt) as can occur in atrial septal defect (ASD).



## Heart morphogenesis *(continued)*

| | | |
|---|---|---|
| Ventricles | ❶ Muscular interventricular septum forms. Opening is called interventricular foramen.<br>❷ Aorticopulmonary septum rotates and fuses with muscular ventricular septum to form membranous interventricular septum, closing interventricular foramen.<br>❸ Growth of endocardial cushions separates atria from ventricles and contributes to both atrial septation and membranous portion of the interventricular septum. | Ventricular septal defect—most common congenital cardiac anomaly, usually occurs in membranous septum. |

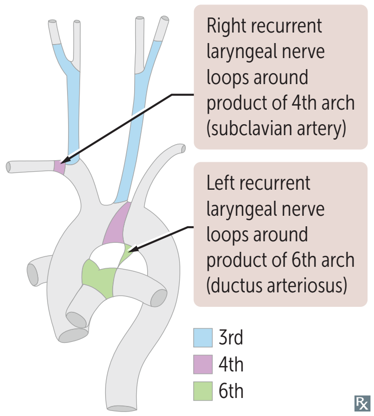



| | | |
|---|---|---|
| Outflow tract formation | Neural crest cell migrations → truncal and bulbar ridges that spiral and fuse to form aorticopulmonary septum → ascending aorta and pulmonary trunk. | Conotruncal abnormalities associated with failure of neural crest cells to migrate:<br>▪ Transposition of great vessels.<br>▪ Tetralogy of Fallot.<br>▪ Persistent truncus arteriosus. |
| Valve development | Aortic/pulmonary: derived from endocardial cushions of outflow tract.<br>Mitral/tricuspid: derived from fused endocardial cushions of the AV canal. | Valvular anomalies may be stenotic, regurgitant, atretic (eg, tricuspid atresia), or displaced (eg, Ebstein anomaly). |

## Aortic arch derivatives

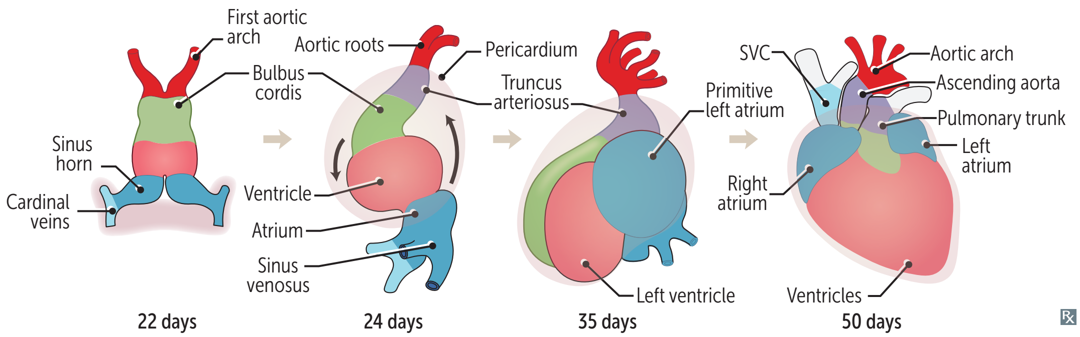
Develop into arterial system.

| | |
|---|---|
| 1st | Part of maxillary artery (branch of external carotid). 1st arch is maximal. |
| 2nd | Stapedial artery and hyoid artery. Second = stapedial. |
| 3rd | Common carotid artery and proximal part of internal carotid artery. C is 3rd letter of alphabet. |
| 4th | On left, aortic arch; on right, proximal part of right subclavian artery. 4th arch (4 limbs) = systemic. |
| 6th | Proximal part of pulmonary arteries and (on left only) ductus arteriosus. 6th arch = pulmonary and the pulmonary-to-systemic shunt (ductus arteriosus). |

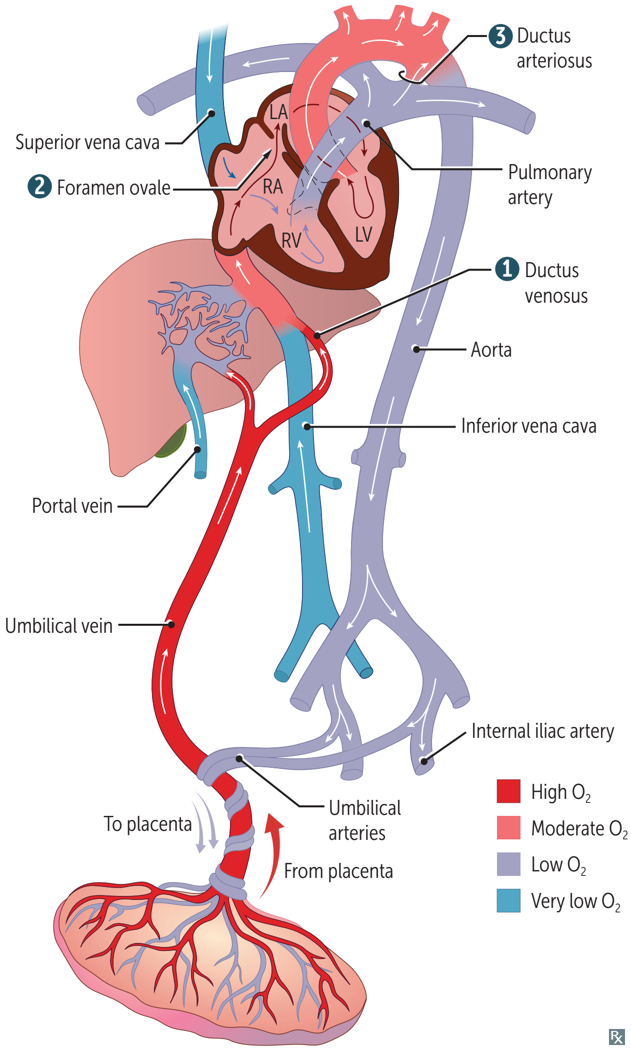


## Heart embryology

| EMBRYONIC STRUCTURE | GIVES RISE TO |
|---|---|
| Truncus arteriosus | Ascending aorta and pulmonary trunk |
| Bulbus cordis | Smooth parts (outflow tract) of left and right ventricles |
| Primitive ventricle | Trabeculated part of left and right ventricles |
| Primitive atrium | Trabeculated part of left and right atria |
| Left horn of sinus venosus | Coronary sinus |
| Right horn of sinus venosus | Smooth part of right atrium (sinus venarum) |
| Endocardial cushion | Atrial septum, membranous interventricular septum; AV and semilunar valves |
| Right common cardinal vein and right anterior cardinal vein | Superior vena cava (SVC) |
| Posterior, subcardinal, and supracardinal veins | Inferior vena cava (IVC) |
| Primitive pulmonary vein | Smooth part of left atrium |



## Fetal circulation




Blood in umbilical vein has a $Po_2$ of ≈ 30 mm Hg and is ≈ 80% saturated with $O_2$. Umbilical arteries have low $O_2$ saturation.

3 important shunts:

1. Blood entering fetus through the umbilical vein is conducted via the **ductus venosus** into the IVC, bypassing hepatic circulation.
2. Most of the highly oxygenated blood reaching the heart via the IVC is directed through the **foramen ovale** into the left atrium.
3. Deoxygenated blood from the SVC passes through the RA → RV → main pulmonary artery → **ductus arteriosus** → descending aorta; shunt is due to high fetal pulmonary artery resistance.

At birth, infant takes a breath → ↓ resistance in pulmonary vasculature → ↑ left atrial pressure vs right atrial pressure→ foramen ovale closes (now called fossa ovalis); ↑ in $O_2$ (from respiration) and ↓ in prostaglandins (from placental separation) → closure of ductus arteriosus.

Indomethacin helps close the patent ductus arteriosus → ligamentum arteriosum (remnant of ductus arteriosus). "Endomethacin" ends the PDA.

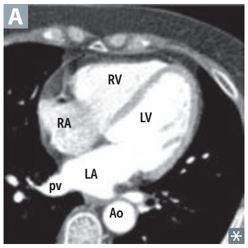
Prostaglandins $E_1$ and $E_2$ kEEp PDA open.

## Fetal-postnatal derivatives

| FETAL STRUCTURE | POSTNATAL DERIVATIVE | NOTES |
|---|---|---|
| **Ductus arteriosus** | Ligamentum arteriosum | Near the left recurrent laryngeal nerve |
| **Ductus venosus** | Ligamentum venosum | |
| **Foramen ovale** | Fossa ovalis | |
| **Allantois → urachus** | Median umbilical ligament | Urachus is part of allantois between bladder and umbilicus |
| **Umbilical arteries** | Medial umbilical ligaments | |
| **Umbilical vein** | Ligamentum teres hepatis (round ligament) | Contained in falciform ligament |

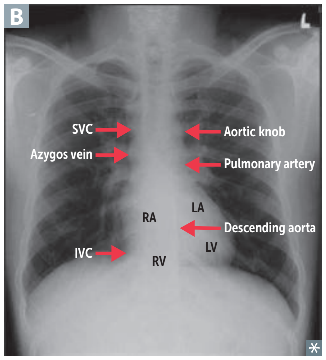
## ▸ CARDIOVASCULAR—ANATOMY

### Anatomy of the heart




LA is the most posterior part of the heart A B; enlargement of the LA (eg, in mitral stenosis) can lead to compression of the esophagus (dysphagia) and/or the left recurrent laryngeal nerve, a branch of the vagus nerve, causing hoarseness (Ortner syndrome).

RV is the most anterior part of the heart and most commonly injured in trauma.




### Pericardium

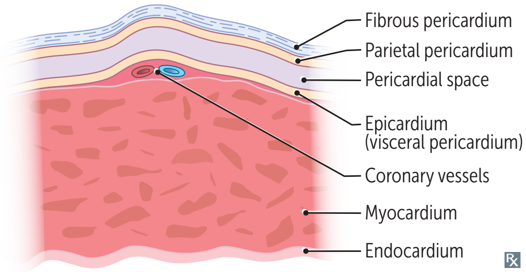
Consists of 3 layers (from outer to inner):

- Fibrous pericardium
- Parietal pericardium
- Epicardium (visceral pericardium)

Pericardial space lies between parietal pericardium and epicardium.

Pericardium innervated by phrenic nerve.

Pericarditis can cause referred pain to the neck, arms, or one or both shoulders (often left).




### Coronary blood supply

LAD and its branches supply anterior 2/3 of interventricular septum, anterolateral papillary muscle, and anterior surface of LV. Most commonly occluded.

PDA supplies posterior 1/3 of interventricular septum, posterior 2/3 walls of ventricles, and posteromedial papillary muscle.

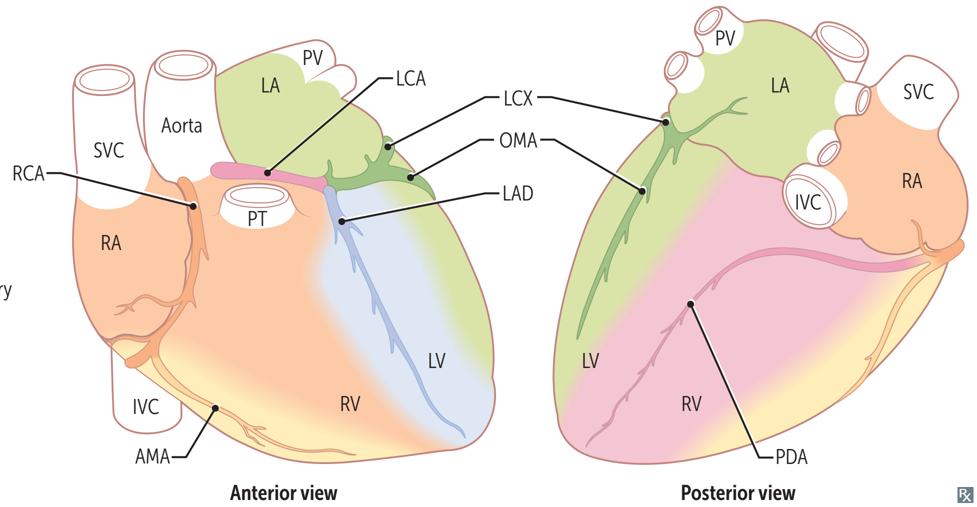
RCA supplies AV node and SA node. Infarct may cause nodal dysfunction (bradycardia or heart block). Right (acute) marginal artery supplies RV.

Dominance:

- Right-dominant circulation (most common) = PDA arises from RCA
- Left-dominant circulation = PDA arises from LCX
- Codominant circulation = PDA arises from both LCX and RCA

Coronary blood flow to LV and interventricular septum peaks in early diastole.

Key:
AMA = Acute marginal artery
LAD = Left anterior descending artery
LCA = Left coronary artery
LCX = Left circumflex artery
OMA = Obtuse marginal artery
PDA = Posterior descending artery
PT = Pulmonary trunk
PV = Pulmonary vein
RCA = Right coronary artery



## ▶ CARDIOVASCULAR—PHYSIOLOGY

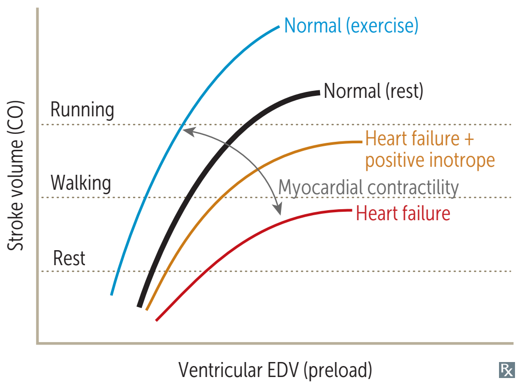
### Cardiac output variables

| | | |
|---|---|---|
| **Stroke volume** | **S**troke **V**olume affected by **C**ontractility, **A**fterload, and **P**reload.<br>↑ SV with:<br>▪ ↑ Contractility (eg, anxiety, exercise)<br>▪ ↑ Preload (eg, early pregnancy)<br>▪ ↓ Afterload | **SV CAP.**<br>A failing heart has ↓ SV (systolic and/or diastolic dysfunction). |
| **Contractility** | Contractility (and SV) ↑ with:<br>▪ Catecholamine stimulation via $\beta_1$ receptor:<br>  ▪ Activated protein kinase A → phospholamban phosphorylation → active $Ca^{2+}$ ATPase → ↑ $Ca^{2+}$ storage in sarcoplasmic reticulum<br>  ▪ Activated protein kinase A → $Ca^{2+}$ channel phosphorylation → ↑ $Ca^{2+}$ entry → ↑ $Ca^{2+}$-induced $Ca^{2+}$ release<br>▪ ↑ intracellular $Ca^{2+}$<br>▪ ↓ extracellular $Na^+$ (↓ activity of $Na^+/Ca^{2+}$ exchanger)<br>▪ Digoxin (blocks $Na^+/K^+$ pump → ↑ intracellular $Na^+$ → ↓ $Na^+/Ca^{2+}$ exchanger activity → ↑ intracellular $Ca^{2+}$) | Contractility (and SV) ↓ with:<br>▪ $\beta_1$-blockade (↓ cAMP)<br>▪ HF with systolic dysfunction<br>▪ Acidosis<br>▪ Hypoxia/hypercapnia (↓ $P_{O_2}$/↑ $P_{CO_2}$)<br>▪ Nondihydropyridine $Ca^{2+}$ channel blockers |
| **Preload** | Preload approximated by ventricular end-diastolic volume (EDV); depends on venous tone and circulating blood volume. | Vasodilators (eg, nitroglycerin) ↓ preload. |
| **Afterload** | Afterload approximated by MAP.<br>↑ wall tension per Laplace's law → ↑ pressure → ↑ afterload.<br><br>LV compensates for ↑ afterload by thickening (hypertrophy) in order to ↓ wall stress. | **A**rterial vasodilators (eg, hydr**ala**zine) ↓ **a**fterload.<br>ACE inhibitors and ARBs ↓ both preload and afterload.<br>Chronic hypertension (↑ MAP) → LV hypertrophy. |
| **Myocardial oxygen demand** | Myo**card**ial $O_2$ demand is ↑ by:<br>▪ ↑ **c**ontractility<br>▪ ↑ **a**fterload (proportional to arterial pressure)<br>▪ ↑ heart **r**ate<br>▪ ↑ **d**iameter of ventricle (↑ wall tension) | Wall tension follows Laplace's law:<br>Wall tension = pressure × radius<br>Wall stress $\propto \dfrac{\text{pressure} \times \text{radius}}{2 \times \text{wall thickness}}$ |

## Cardiac output equations

| | EQUATION | NOTES |
|---|---|---|
| **Stroke volume** | SV = EDV – ESV | ESV = end-systolic volume. |
| **Ejection fraction** | $EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$ | EF is an index of ventricular contractility (↓ in systolic HF; usually normal in diastolic HF). |
| **Cardiac output** | CO = SV × HR<br><br>Fick principle:<br>$CO = \frac{\text{rate of } O_2 \text{ consumption}}{(\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content})}$ | In early stages of exercise, CO maintained by ↑ HR and ↑ SV. In later stages, CO maintained by ↑ HR only (SV plateaus).<br>Diastole is shortened with ↑↑ HR (eg, ventricular tachycardia) → ↓ diastolic filling time → ↓ SV → ↓ CO. |
| **Pulse pressure** | PP = systolic blood pressure (SBP) – diastolic blood pressure (DBP) | PP directly proportional to SV and inversely proportional to arterial compliance.<br>↑ PP in hyperthyroidism, aortic regurgitation, aortic stiffening (isolated systolic hypertension in elderly), obstructive sleep apnea (↑ sympathetic tone), anemia, exercise (transient).<br>↓ PP in aortic stenosis, cardiogenic shock, cardiac tamponade, advanced HF. |
| **Mean arterial pressure** | MAP = CO × total peripheral resistance (TPR) | MAP (at resting HR) = 2/3 DBP + 1/3 SBP = DBP + 1/3 PP. |

## Starling curves




Force of contraction is proportional to end-diastolic length of cardiac muscle fiber (preload).

↑ contractility with catecholamines, positive inotropes (eg, dobutamine, milrinone, digoxin).

↓ contractility with loss of functional myocardium (eg, MI), β-blockers (acutely), nondihydropyridine $Ca^{2+}$ channel blockers, HF.

## Resistance, pressure, flow

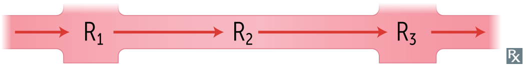
Volumetric flow rate (Q) = flow velocity (v) × cross-sectional area (A)

Resistance

$$= \frac{\text{driving pressure } (\Delta P)}{Q} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$$

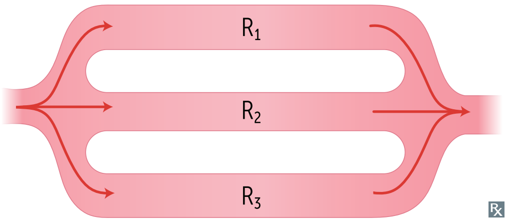
Total resistance of vessels in series:

$R_T = R_1 + R_2 + R_3 \ldots$




Total resistance of vessels in parallel:

$$\frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} \ldots$$




$Q \propto r^4$

$R \propto 1/r^4$

Capillaries have highest total cross-sectional area and lowest flow velocity.

Pressure gradient drives flow from high pressure to low pressure.

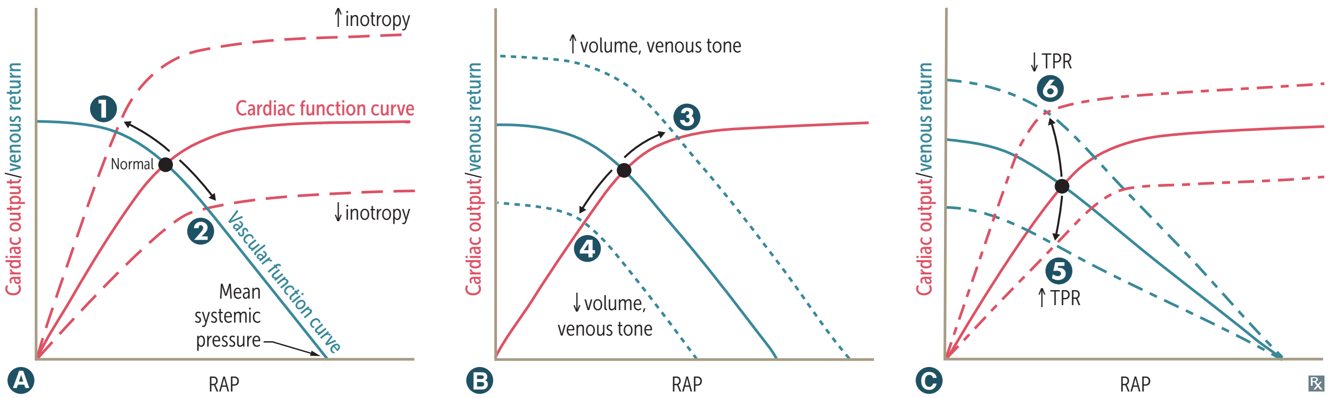
Arterioles account for most of TPR. Veins provide most of blood storage capacity.

Viscosity depends mostly on hematocrit.

Viscosity ↑ in hyperproteinemic states (eg, multiple myeloma), polycythemia.

Viscosity ↓ in anemia.

## Cardiac and vascular function curves

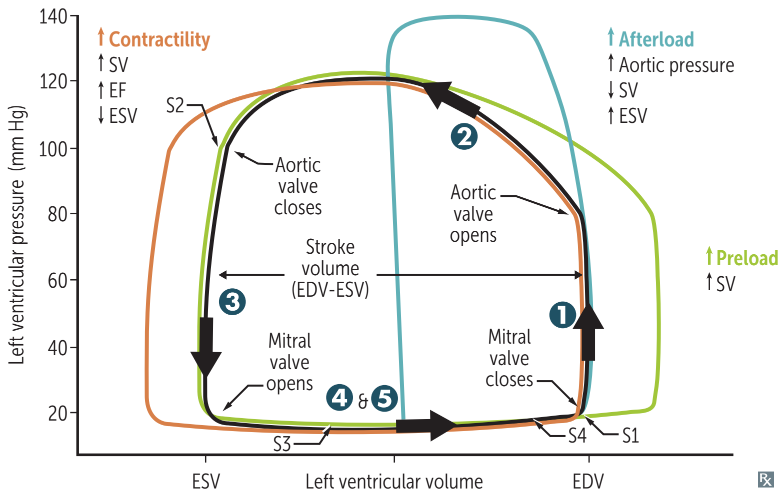



Intersection of curves = operating point of heart (ie, venous return and CO are equal, as circulatory system is a closed system).

| GRAPH | EFFECT | EXAMPLES |
|---|---|---|
| **A Inotropy** | Changes in contractility → altered SV → altered CO/VR and RA pressure (RAP) | 1 Catecholamines, dobutamine, milrinone, digoxin, exercise ⊕<br>2 HF with reduced EF, narcotic overdose, sympathetic inhibition ⊖ |
| **B Venous return** | Changes in circulating volume → altered RAP → altered SV → change in CO | 3 Fluid infusion, sympathetic activity ⊕<br>4 Acute hemorrhage, spinal anesthesia ⊖ |
| **C Total peripheral resistance** | Changes in TPR → altered CO<br>Change in RAP unpredictable | 5 Vasopressors ⊕<br>6 Exercise, arteriovenous shunt ⊖ |

Changes often occur in tandem, and may be reinforcing (eg, exercise ↑ inotropy and ↓ TPR to maximize CO) or compensatory (eg, HF ↓ inotropy → fluid retention to ↑ preload to maintain CO).

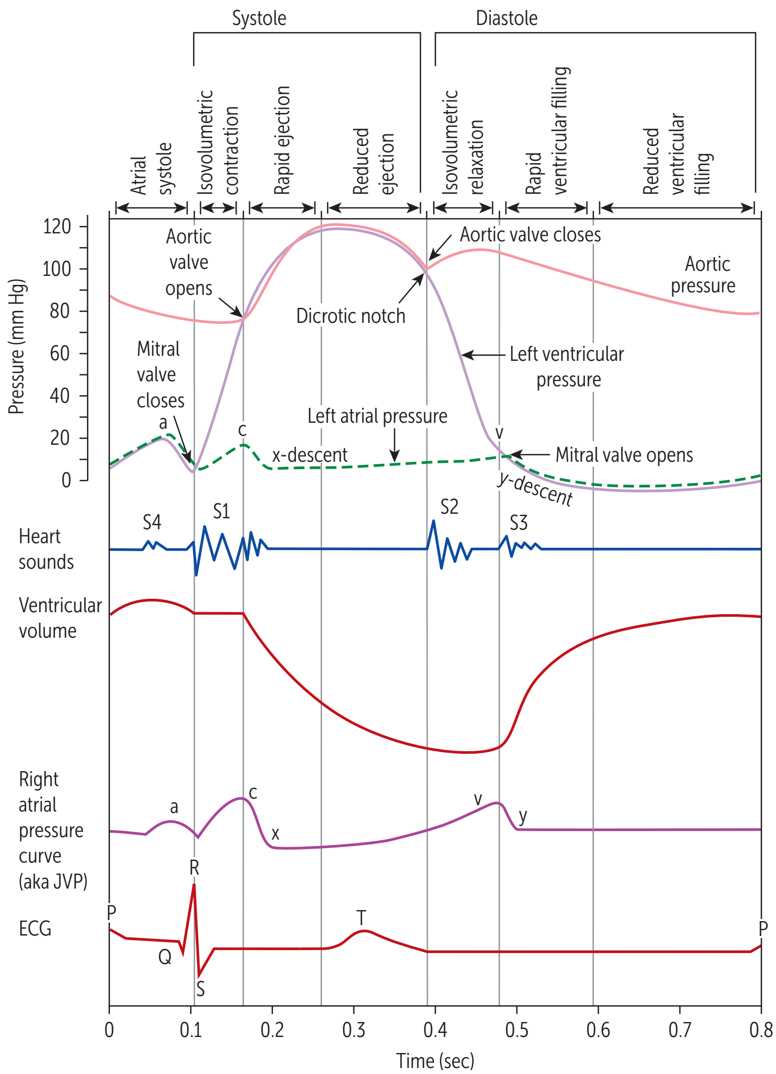
## Pressure-volume loops and cardiac cycle




The black loop represents normal cardiac physiology.

Phases—left ventricle:

1. Isovolumetric contraction—period between mitral valve closing and aortic valve opening; period of highest $O_2$ consumption
2. Systolic ejection—period between aortic valve opening and closing
3. Isovolumetric relaxation—period between aortic valve closing and mitral valve opening
4. Rapid filling—period just after mitral valve opening
5. Reduced filling—period just before mitral valve closing




Heart sounds:

S1—mitral and tricuspid valve closure. Loudest at mitral area.

S2—aortic and pulmonary valve closure. Loudest at left upper sternal border.

S3—in early diastole during rapid ventricular filling phase. Best heard at apex with patient in left lateral decubitus position. Associated with ↑ filling pressures (eg, MR, AR, HF, thyrotoxicosis) and more common in dilated ventricles (but can be normal in children, young adults, athletes, and pregnancy). Turbulence caused by blood from LA mixing with ↑ ESV.

S4—in late diastole ("atrial kick"). Turbulence caused by blood entering stiffened LV. Best heard at apex with patient in left lateral decubitus position. High atrial pressure. Associated with ventricular noncompliance (eg, hypertrophy). Can be normal in older adults. Considered abnormal if palpable.

Jugular venous pulse (JVP):

a wave—atrial contraction. Absent in atrial fibrillation.

c wave—RV contraction (closed tricuspid valve bulging into atrium).

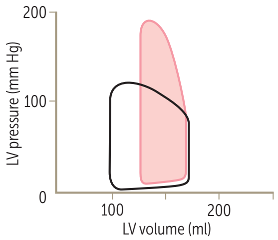
x descent—atrial relaxation and downward displacement of closed tricuspid valve during rapid ventricular ejection phase. Reduced or absent in tricuspid regurgitation and right HF because pressure gradients are reduced.

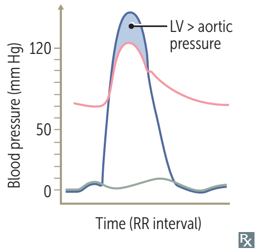
v wave—↑ RA pressure due to ↑ volume against closed tricuspid valve.

y descent—RA emptying into RV. Prominent in constrictive pericarditis, absent in cardiac tamponade.

## Pressure-volume loops and valvular disease

### Aortic stenosis

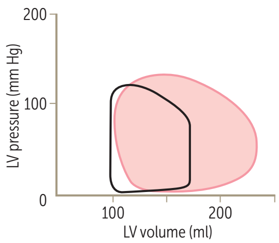


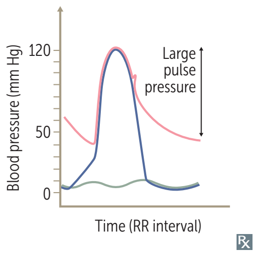




↑ LV pressure
↑ ESV
No change in EDV (if mild)
↓ SV

Ventricular hypertrophy → ↓ ventricular compliance → ↑ EDP for given EDV

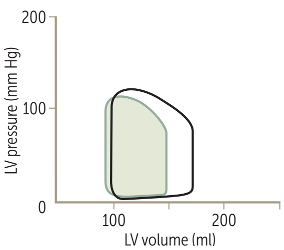
### Aortic regurgitation

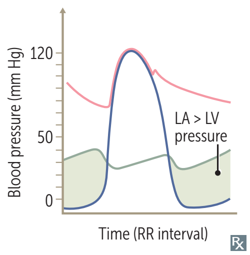



No true isovolumetric phase
↑ EDV
↑ SV
Loss of dichrotic notch

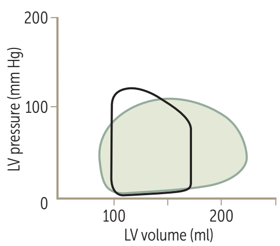
### Mitral stenosis

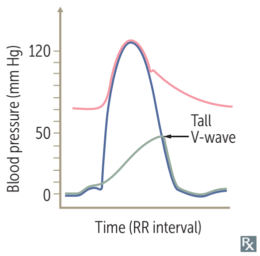



↑ LA pressure
↓ EDV because of impaired ventricular filling
↓ ESV
↓ SV

### Mitral regurgitation



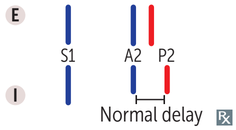




No true isovolumetric phase
↓ ESV due to ↓ resistance and ↑ regurgitation into LA during systole
↑ EDV due to ↑ LA volume/pressure from regurgitation → ↑ ventricular filling
↑ SV (forward flow into systemic circulation plus backflow into LA)

## Splitting of S2

### Physiologic splitting

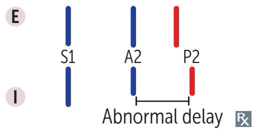
Inspiration → drop in intrathoracic pressure → ↑ venous return → ↑ RV filling → ↑ RV stroke volume → ↑ RV ejection time → delayed closure of pulmonic valve.
↓ pulmonary impedance (↑ capacity of the pulmonary circulation) also occurs during inspiration, which contributes to delayed closure of pulmonic valve.




E = Expiration
I = Inspiration

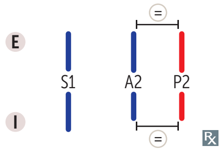
### Wide splitting

Seen in conditions that delay RV emptying (eg, pulmonic stenosis, right bundle branch block). Causes delayed pulmonic sound (especially on inspiration). An exaggeration of normal splitting.



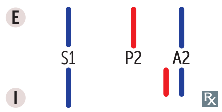

### Fixed splitting

Heard in ASD. ASD → left-to-right shunt → ↑ RA and RV volumes → ↑ flow through pulmonic valve → delayed pulmonic valve closure (independent of respiration).

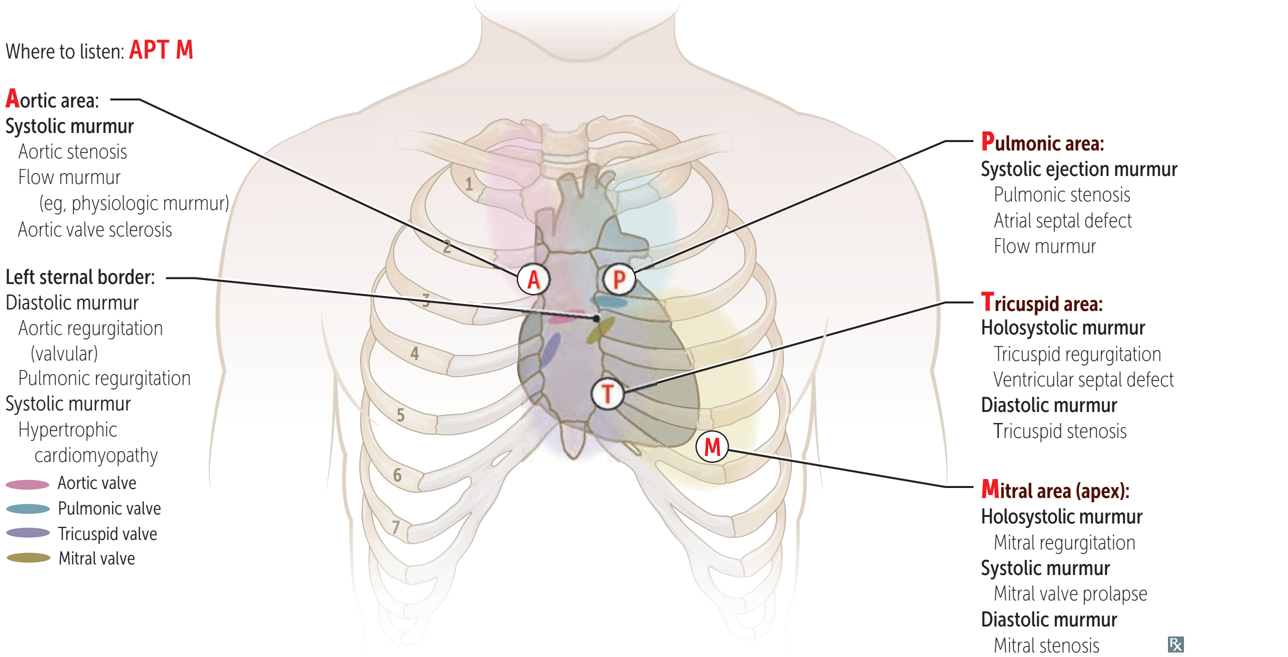



### Paradoxical splitting

Heard in conditions that delay aortic valve closure (eg, aortic stenosis, left bundle branch block). Normal order of semilunar valve closure is reversed: in **pa**radoxical splitting **P**2 occurs before **A**2. On inspiration, P2 closes later and moves closer to A2, "paradoxically" eliminating the split. On expiration, the split can be heard (opposite to physiologic splitting).



### Auscultation of the heart

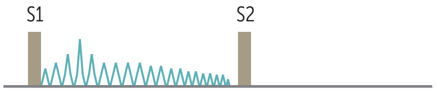



| MANEUVER | CARDIOVASCULAR CHANGES | MURMURS THAT INCREASE WITH MANEUVER | MURMURS THAT DECREASE WITH MANEUVER |
|---|---|---|---|
| Standing Valsalva (strain phase) | ↓ preload (↓ LV volume) | MVP (↓ LV volume) with earlier midsystolic click<br>HCM (↓ LV volume) | Most murmurs (↓ flow through stenotic or regurgitant valve) |
| Passive leg raise | ↑ preload (↑ LV volume) | Most murmurs (↑ flow through stenotic or regurgitant valve) | MVP (↑ LV volume) with later midsystolic click<br>HCM (↑ LV volume) |
| Squatting | ↑ preload, ↑ afterload (↑ LV volume) | | |
| Hand grip | ↑↑ afterload → ↑ reverse flow across aortic valve (↑ LV volume) | Most other left-sided murmurs (AR, MR, VSD) | AS (↓ transaortic valve pressure gradient)<br>HCM (↑ LV volume) |
| Inspiration | ↑ venous return to right heart, ↓ venous return to left heart | Most right-sided murmurs | Most left-sided murmurs |

## Heart murmurs

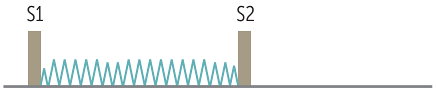
### Systolic

**Aortic stenosis**




Crescendo-decrescendo systolic ejection murmur and soft S2 (ejection click may be present). LV >> aortic pressure during systole. Loudest at heart base; radiates to carotids. "Pulsus parvus et tardus"—pulses are weak with a delayed peak. Can lead to **S**yncope, **A**ngina, and **D**yspnea on exertion (**SAD**). Most commonly due to age-related calcification in older patients (> 60 years old) or in younger patients with early-onset calcification of bicuspid aortic valve.

**Mitral/tricuspid regurgitation**



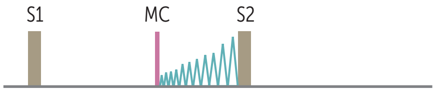

Holosystolic, high-pitched "blowing murmur."

Mitral—loudest at apex and radiates toward axilla. MR is often due to ischemic heart disease (post-MI), MVP, LV dilatation.

Tricuspid—loudest at tricuspid area. TR commonly caused by RV dilatation.

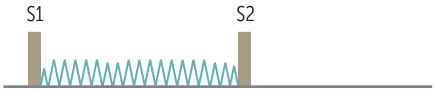
Rheumatic fever and infective endocarditis can cause either MR or TR.

**Mitral valve prolapse**




Late systolic crescendo murmur with midsystolic click (MC) due to sudden tensing of chordae tendineae as mitral leaflets prolapse into the LA (**c**hordae cause **c**rescendo with **c**lick). Best heard over apex. Loudest just before S2. Usually benign. Can predispose to infective endocarditis. Can be caused by myxomatous degeneration (1° or 2° to connective tissue disease such as Marfan or Ehlers-Danlos syndrome), rheumatic fever (particularly in developing countries), chordae rupture.

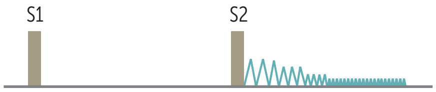
**Ventricular septal defect**




Holosystolic, harsh-sounding murmur. Loudest at tricuspid area. Larger VSDs have a lower intensity murmur than smaller VSDs.

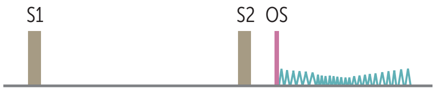
### Diastolic

**Aortic regurgitation**




High-pitched "blowing" early diastolic decrescendo murmur. Best heard at base (aortic root dilation) or left sternal border (valvular disease). Long diastolic murmur, hyperdynamic pulse, and head bobbing when severe and chronic. Wide pulse pressure. Causes include **B**icuspid aortic valve, **E**ndocarditis, **A**ortic root dilation, **R**heumatic fever (**BEAR**). Progresses to left HF.

**Mitral stenosis**

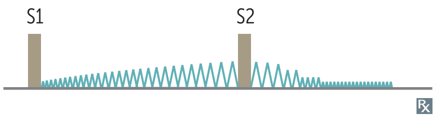



Follows opening snap (OS; due to abrupt halt in leaflet motion in diastole, after rapid opening due to fusion at leaflet tips). Delayed rumbling mid-to-late diastolic murmur (↓ interval between S2 and OS correlates with ↑ severity). LA >> LV pressure during diastole.

Often a late (and highly specific) sequela of rheumatic fever. Chronic MS can result in pulmonary congestion/hypertension and LA dilation → atrial fibrillation and Ortner syndrome.

### Continuous

**Patent ductus arteriosus**



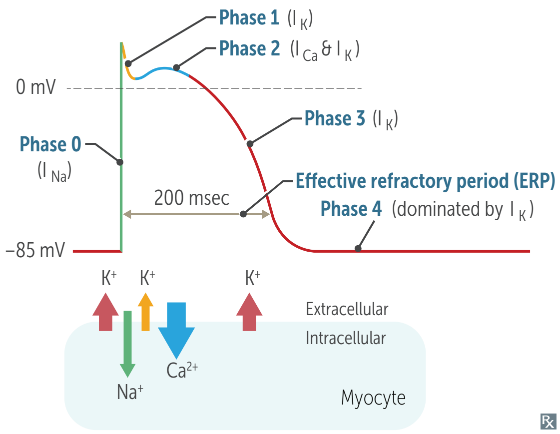

Continuous **machine**-like murmur. Best heard at left infraclavicular area. Loudest at S2. Often due to congenital rubella or prematurity.

You need a **patent** for that **machine**.

**Myocardial action potential**

**Phase 0** = rapid upstroke and depolarization—voltage-gated $Na^+$ channels open.
**Phase 1** = initial repolarization—inactivation of voltage-gated $Na^+$ channels. Voltage-gated $K^+$ channels begin to open.
**Phase 2** = plateau—$Ca^{2+}$ influx through voltage-gated $Ca^{2+}$ channels balances $K^+$ efflux. $Ca^{2+}$ influx triggers $Ca^{2+}$ release from sarcoplasmic reticulum and myocyte contraction (excitation-contraction coupling).
**Phase 3** = rapid repolarization—massive $K^+$ efflux due to opening of voltage-gated slow delayed-rectifier $K^+$ channels and closure of voltage-gated $Ca^{2+}$ channels.
**Phase 4** = resting potential—high $K^+$ permeability through $K^+$ channels.

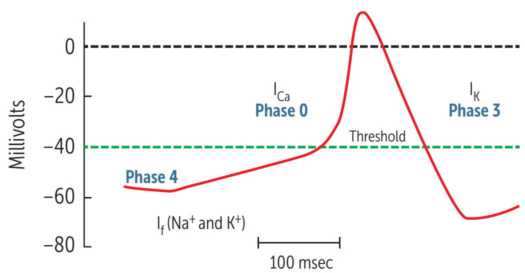
In contrast to skeletal muscle:
- Cardiac muscle action potential has a plateau due to $Ca^{2+}$ influx and $K^+$ efflux.
- Cardiac muscle contraction requires $Ca^{2+}$ influx from ECF to induce $Ca^{2+}$ release from sarcoplasmic reticulum ($Ca^{2+}$-induced $Ca^{2+}$ release).
- Cardiac myocytes are electrically coupled to each other by gap junctions.




Occurs in all cardiac myocytes except for those in the SA and AV nodes.

**Pacemaker action potential**

Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:
**Phase 0** = upstroke—opening of voltage-gated $Ca^{2+}$ channels. Fast voltage-gated $Na^+$ channels are permanently inactivated because of the less negative resting potential of these cells. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles.
Phases 1 and 2 are absent.
**Phase 3** = repolarization—inactivation of the $Ca^{2+}$ channels and ↑ activation of $K^+$ channels → ↑ $K^+$ efflux.
**Phase 4** = slow spontaneous diastolic depolarization due to $I_f$ ("funny current"). $I_f$ channels responsible for a slow, mixed $Na^+/K^+$ inward current; different from $I_{Na}$ in phase 0 of ventricular action potential. Accounts for automaticity of SA and AV nodes. The slope of phase 4 in the SA node determines HR. ACh/adenosine ↓ the rate of diastolic depolarization and ↓ HR, while catecholamines ↑ depolarization and ↑ HR. Sympathetic stimulation ↑ the chance that $I_f$ channels are open and thus ↑ HR.



## Electrocardiogram

Conduction pathway: SA node → atria → AV node → bundle of His → right and left bundle branches → Purkinje fibers → ventricles; left bundle branch divides into left anterior and posterior fascicles.

SA node—located at junction of RA and SVC; "pacemaker" inherent dominance with slow phase of upstroke.

AV node—located in posteroinferior part of interatrial septum. Blood supply usually from RCA. 100-msec delay allows time for ventricular filling.

Pacemaker rates: SA > AV > bundle of His/Purkinje/ventricles.

Speed of conduction: **His-Purkinje** > **Atria** > **Ventricles** > **AV** node. **He Parks At Ventura AVenue.**

P wave—atrial depolarization.

PR interval—time from start of atrial depolarization to start of ventricular depolarization (normally 120-200 msec).

QRS complex—ventricular depolarization (normally < 100 msec).

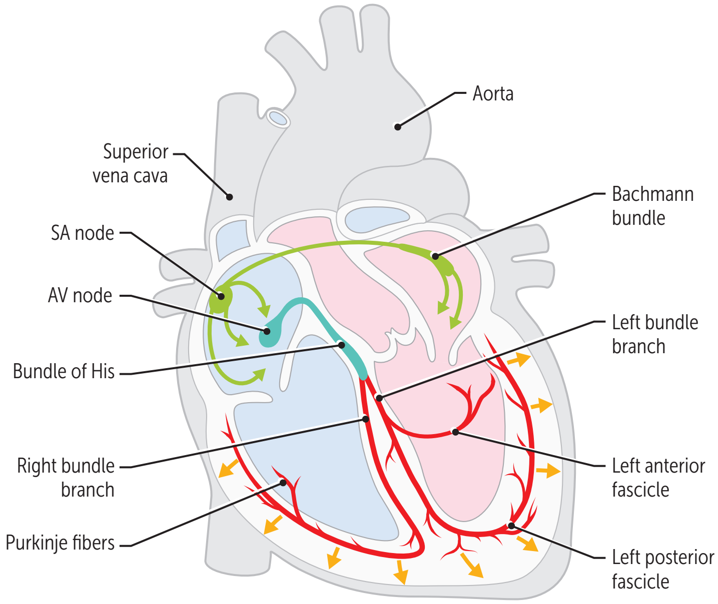
QT interval—ventricular depolarization, mechanical contraction of the ventricles, ventricular repolarization.

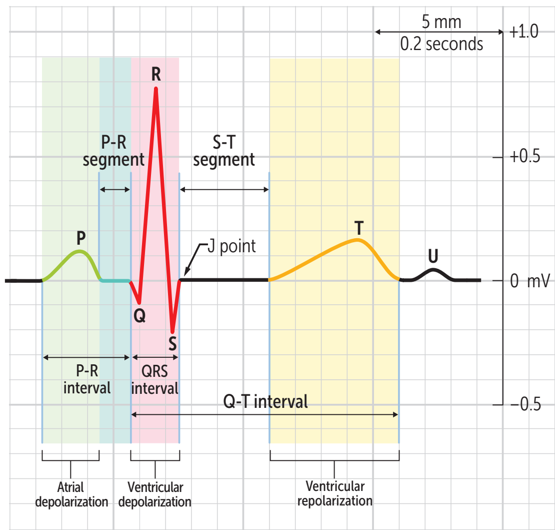
T wave—ventricular repolarization. T-wave inversion may indicate ischemia or recent MI.

J point—junction between end of QRS complex and start of ST segment.

ST segment—isoelectric, ventricles depolarized.

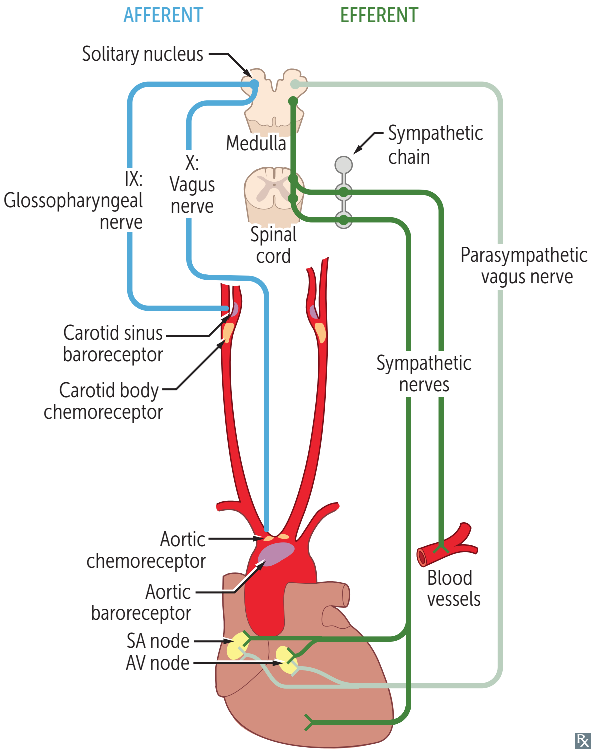
**U** wave—prominent in hypokalemia (think hyp"**U**"kalemia), bradycardia.



| | |
|---|---|
| **Atrial natriuretic peptide** | Released from **atrial myocytes** in response to ↑ blood volume and atrial pressure. Acts via cGMP. Causes vasodilation and ↓ $Na^+$ reabsorption at the renal collecting tubule. Dilates afferent renal arterioles and constricts efferent arterioles, promoting diuresis and contributing to "aldosterone escape" mechanism. |
| **B-type (brain) natriuretic peptide** | Released from **ventricular myocytes** in response to ↑ tension. Similar physiologic action to ANP, with longer half-life. BNP blood test used for diagnosing HF (very good negative predictive value). Available in recombinant form (nesiritide) for treatment of HF. |

## Baroreceptors and chemoreceptors



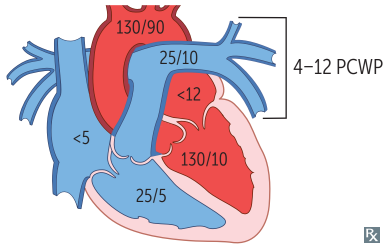

**Receptors:**
- Aortic arch transmits via vagus nerve to solitary nucleus of medulla (responds to changes in BP).
- Carotid sinus (dilated region superior to bifurcation of carotid arteries) transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to changes in BP).

**Chemoreceptors:**
- Peripheral—carotid and aortic bodies are stimulated by ↑ $P_{CO_2}$, ↓ pH of blood, and ↓ $P_{O_2}$ (< 60 mm Hg).
- Central—are stimulated by changes in pH and $P_{CO_2}$ of brain interstitial fluid, which in turn are influenced by arterial $CO_2$ as $H^+$ cannot cross the blood-brain barrier. Do not directly respond to $P_{O_2}$. Central chemoreceptors become less responsive with chronically ↑ $P_{CO_2}$ (eg, COPD) → ↑ dependence on peripheral chemoreceptors to detect ↓ $O_2$ to drive respiration.

**Baroreceptors:**
- Hypotension—↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, ↑ HR, ↑ contractility, ↑ BP. Important in the response to severe hemorrhage.
- Carotid massage—↑ pressure on carotid sinus → ↑ stretch → ↑ afferent baroreceptor firing → ↑ AV node refractory period → ↓ HR.
- Component of Cushing reflex (triad of hypertension, bradycardia, and respiratory depression)—↑ intracranial pressure constricts arterioles → cerebral ischemia → ↑ $pCO_2$ and ↓ pH → central reflex sympathetic ↑ in perfusion pressure (hypertension) → ↑ stretch → peripheral reflex baroreceptor–induced bradycardia.

**Normal cardiac pressures**

Pulmonary capillary wedge pressure (PCWP; in mm Hg) is a good approximation of left atrial pressure. In mitral stenosis, PCWP > LV end diastolic pressure. PCWP is measured with pulmonary artery catheter (Swan-Ganz catheter).




**Autoregulation**

How blood flow to an organ remains constant over a wide range of perfusion pressures.

| ORGAN | FACTORS DETERMINING AUTOREGULATION | |
|---|---|---|
| Lungs | Hypoxia causes vasoconstriction | The pulmonary vasculature is unique in that alveolar hypoxia causes vasoconstriction so that only well-ventilated areas are perfused. In other organs, hypoxia causes vasodilation |
| Heart | Local metabolites (vasodilatory): NO, $CO_2$, ↓ $O_2$ | |
| Brain | Local metabolites (vasodilatory): $CO_2$ (pH) | |
| Kidneys | Myogenic and tubuloglomerular feedback | |
| Skeletal muscle | Local metabolites during exercise (vasodilatory): **C**$O_2$, **H**$^+$, **A**denosine, **L**actate, **K**$^+$<br>At rest: sympathetic tone in arteries | **CHALK** |
| Skin | Sympathetic vasoconstriction most important mechanism for temperature control | |

**Capillary fluid exchange**

Starling forces determine fluid movement through capillary membranes:

- $P_c$ = capillary hydrostatic pressure—pushes fluid out of capillary
- $P_i$ = interstitial hydrostatic pressure—pushes fluid into capillary
- $\pi_c$ = plasma oncotic pressure—pulls fluid into capillary
- $\pi_i$ = interstitial fluid oncotic pressure—pulls fluid out of capillary

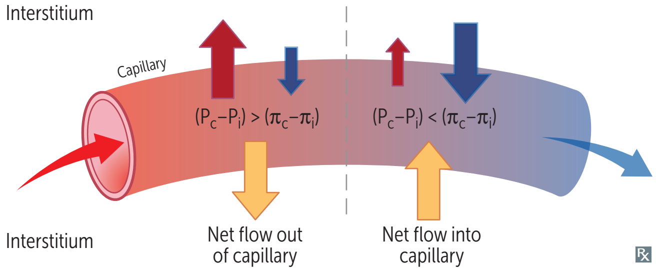
$J_v$ = net fluid flow = $K_f [(P_c - P_i) - \sigma(\pi_c - \pi_i)]$

$K_f$ = capillary permeability to fluid

$\sigma$ = reflection coefficient (measure of capillary permeability to protein)

Edema—excess fluid outflow into interstitium commonly caused by:

- ↑ capillary pressure (↑ $P_c$; eg, HF)
- ↑ capillary permeability (↑ $K_f$; eg, toxins, infections, burns)
- ↑ interstitial fluid oncotic pressure (↑ $\pi_i$; eg, lymphatic blockage)
- ↓ plasma proteins (↓ $\pi_c$; eg, nephrotic syndrome, liver failure, protein malnutrition)



## ▸ CARDIOVASCULAR—PATHOLOGY

### Congenital heart diseases

**RIGHT-TO-LEFT SHUNTS**

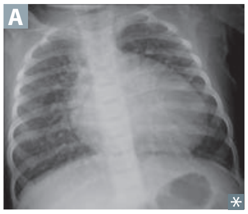
Early cyanosis—"blue babies." Often diagnosed prenatally or become evident immediately after birth. Usually require urgent surgical treatment and/or maintenance of a PDA.

The 5 T's:
1. Truncus arteriosus (1 vessel)
2. Transposition (2 switched vessels)
3. Tricuspid atresia (3 = Tri)
4. Tetralogy of Fallot (4 = Tetra)
5. TAPVR (5 letters in the name)

**Persistent truncus arteriosus**

Truncus arteriosus fails to divide into pulmonary trunk and aorta due to failure of aorticopulmonary septum formation; most patients have accompanying VSD.

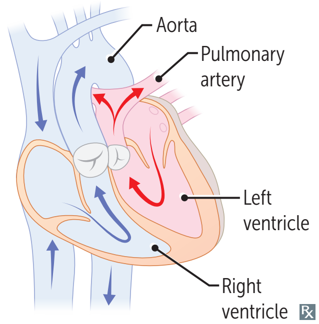
**D-transposition of great vessels**




Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) → separation of systemic and pulmonary circulations. Not compatible with life unless a shunt is present to allow mixing of blood (eg, VSD, PDA, or patent foramen ovale).

Due to failure of the aorticopulmonary septum to spiral ("egg on a string" appearance on CXR) A.

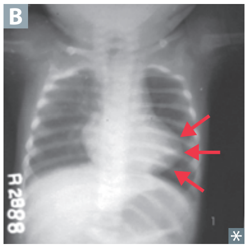
Without surgical intervention, most infants die within the first few months of life.




**Tricuspid atresia**

Absence of tricuspid valve and hypoplastic RV; requires both ASD and VSD for viability.

**Tetralogy of Fallot**




Caused by anterosuperior displacement of the infundibular septum. Most common cause of early childhood cyanosis.

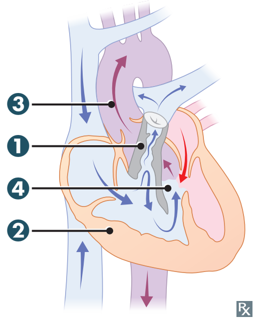
1. Pulmonary infundibular stenosis (most important determinant for prognosis)
2. Right ventricular hypertrophy (RVH)—boot-shaped heart on CXR B
3. Overriding aorta
4. VSD

Pulmonary stenosis forces right-to-left flow across VSD → RVH, "tet spells" (often caused by crying, fever, and exercise due to exacerbation of RV outflow obstruction).

PROVe.

Squatting: ↑ SVR, ↓ right-to-left shunt, improves cyanosis.

Associated with 22q11 syndromes.




**Total anomalous pulmonary venous return**

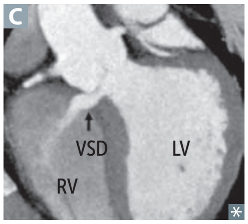
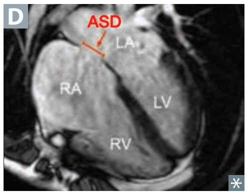
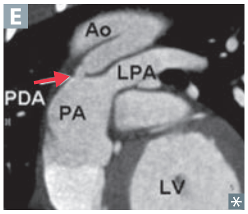
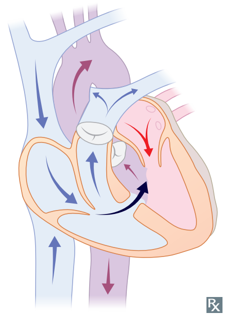
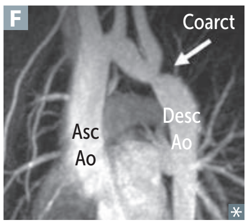
Pulmonary veins drain into right heart circulation (SVC, coronary sinus, etc); associated with ASD and sometimes PDA to allow for right-to-left shunting to maintain CO.

**Ebstein anomaly**

Displacement of tricuspid valve leaflets downward into RV, artificially "atrializing" the ventricle. Associated with tricuspid regurgitation, accessory conduction pathways, right-sided HF.

Can be caused by lithium exposure in utero.

## Congenital heart diseases *(continued)*

| | | |
|---|---|---|
| LEFT-TO-RIGHT SHUNTS | Acyanotic at presentation; cyanosis may occur years later. Frequency: VSD > ASD > PDA. | Right-to-left shunts: early cyanosis.<br>Left-to-right shunts: "later" cyanosis. |
| **Ventricular septal defect**<br> | Asymptomatic at birth, may manifest weeks later or remain asymptomatic throughout life. Most self resolve; larger lesions C may lead to LV overload and HF. | $O_2$ saturation ↑ in RV and pulmonary artery. |
| **Atrial septal defect**<br> | Defect in interatrial septum D; wide, fixed split S2. Ostium secundum defects most common and usually an isolated finding; ostium primum defects rarer and usually occur with other cardiac anomalies. Symptoms range from none to HF. Distinct from patent foramen ovale in that septa are missing tissue rather than unfused. | $O_2$ saturation ↑ in RA, RV, and pulmonary artery. May lead to paradoxical emboli (systemic venous emboli use ASD to bypass lungs and become systemic arterial emboli). Associated with Down syndrome. |
| **Patent ductus arteriosus**<br> | In fetal period, shunt is right to left (normal). In neonatal period, ↓ pulmonary vascular resistance → shunt becomes left to right → progressive RVH and/or LVH and HF.<br>Associated with a continuous, "machine-like" murmur. Patency is maintained by PGE synthesis and low $O_2$ tension. Uncorrected PDA E can eventually result in late cyanosis in the lower extremities (differential cyanosis). | PDA is normal in utero and normally closes only after birth. |
| **Eisenmenger syndrome** | Uncorrected left-to-right shunt (VSD, ASD, PDA) → ↑ pulmonary blood flow → pathologic remodeling of vasculature → pulmonary arterial hypertension. RVH occurs to compensate → shunt becomes right to left. Causes late cyanosis, clubbing, and polycythemia. Age of onset varies depending on size and severity of initial left-to-right shunt. |  |
| OTHER ANOMALIES | | |
| **Coarctation of the aorta**<br> | Aortic narrowing F near insertion of ductus arteriosus ("juxtaductal"). Associated with bicuspid aortic valve, other heart defects, and Turner syndrome. Hypertension in upper extremities and weak, delayed pulse in lower extremities (brachial-femoral delay). With age, intercostal arteries enlarge due to collateral circulation; arteries erode ribs → notched appearance on CXR.<br>Complications include HF, ↑ risk of cerebral hemorrhage (berry aneurysms), aortic rupture, and possible endocarditis. | |

## Congenital cardiac defect associations

| ASSOCIATION | DEFECT |
|---|---|
| Prenatal alcohol exposure (fetal alcohol syndrome) | VSD, PDA, ASD, tetralogy of Fallot |
| Congenital rubella | PDA, pulmonary artery stenosis, septal defects |
| Down syndrome | AV septal defect (endocardial cushion defect), VSD, ASD |
| Infant of patient with diabetes during pregnancy | Transposition of great vessels, VSD |
| Marfan syndrome | MVP, thoracic aortic aneurysm and dissection, aortic regurgitation |
| Prenatal lithium exposure | Ebstein anomaly |
| Turner syndrome | Bicuspid aortic valve, coarctation of aorta |
| Williams syndrome | Supravalvular aortic stenosis |
| 22q11 syndromes | Truncus arteriosus, tetralogy of Fallot |

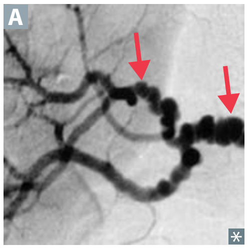
## Hypertension

Persistent systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 80 mm Hg.

**RISK FACTORS**

↑ age, obesity, diabetes, physical inactivity, high-sodium diet, excess alcohol intake, tobacco smoking, family history; incidence greatest in Black > White > Asian populations.

**FEATURES**




90% of hypertension is 1° (essential) and related to ↑ CO or ↑ TPR. Remaining 10% mostly 2° to renal/renovascular diseases such as fibromuscular dysplasia (characteristic "string of beads" appearance of renal artery A, usually seen in adult females) and atherosclerotic renal artery stenosis or to 1° hyperaldosteronism.

**Hypertensive urgency**—severe (≥ 180/≥ 120 mm Hg) hypertension without acute end-organ damage.

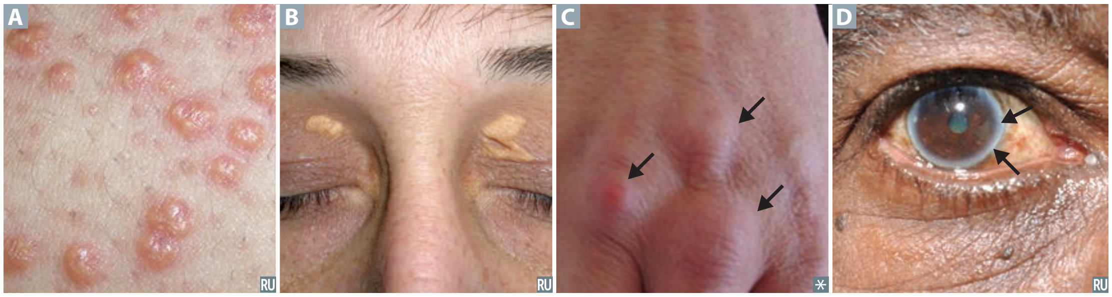
**Hypertensive emergency**—severe hypertension with evidence of acute end-organ damage (eg, encephalopathy, stroke, retinal hemorrhages and exudates, papilledema, MI, HF, aortic dissection, kidney injury, microangiopathic hemolytic anemia, eclampsia).

**PREDISPOSES TO**

CAD, LVH, HF, atrial fibrillation; aortic dissection, aortic aneurysm; stroke; CKD (hypertensive nephropathy); retinopathy.

## Hyperlipidemia signs

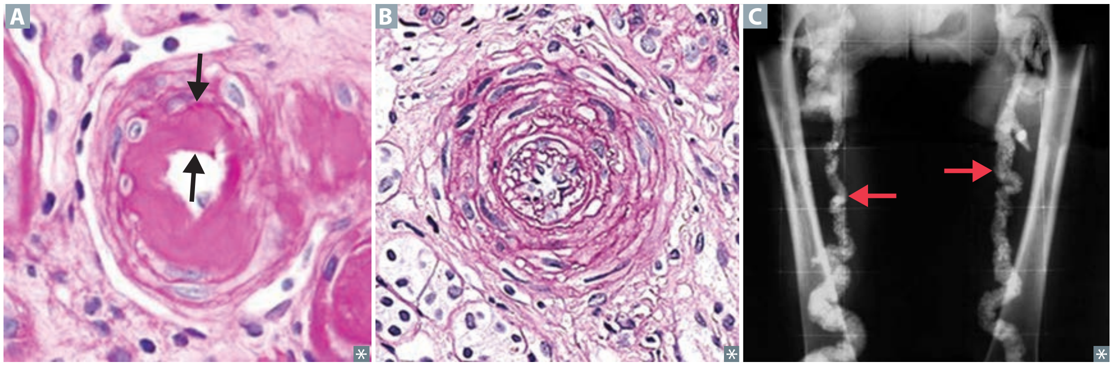
| | |
|---|---|
| **Xanthomas** | Plaques or nodules composed of lipid-laden histiocytes in skin A, especially the eyelids (xanthelasma B). |
| **Tendinous xanthoma** | Lipid deposit in tendon C, especially Achilles tendon and finger extensors. |
| **Corneal arcus** | Lipid deposit in cornea. Common in elderly (arcus senilis D), but appears earlier in life with hypercholesterolemia. |



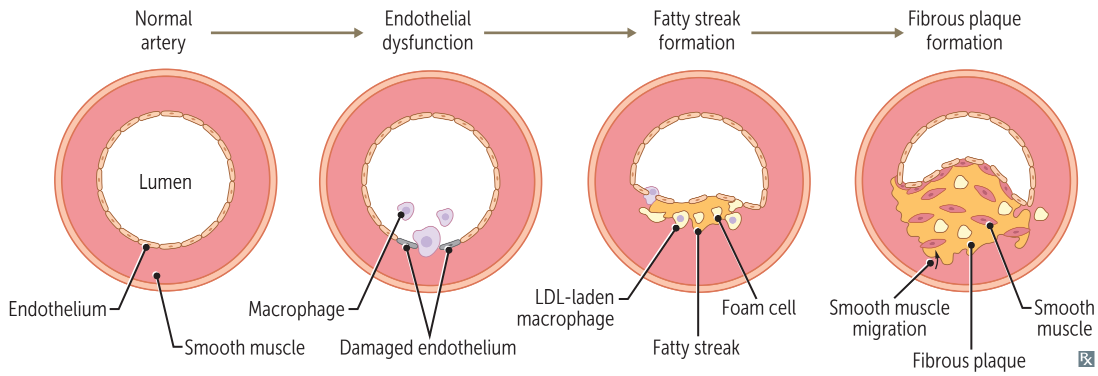

## Arteriosclerosis

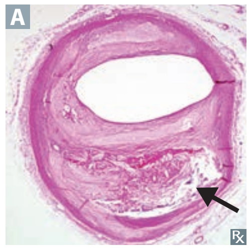
Hardening of arteries, with arterial wall thickening and loss of elasticity.

| | |
|---|---|
| **Arteriolosclerosis** | Common. Affects small arteries and arterioles. Two types:<br>▪ Hyaline—thickening of vessel walls 2° to plasma protein leak into endothelium in essential hypertension or diabetes mellitus A.<br>▪ Hyperplastic—"onion skinning" B in severe hypertension with proliferation of smooth muscle cells. |
| **Mönckeberg sclerosis** | Also called medial calcific sclerosis. Uncommon. Affects medium-sized arteries. Calcification of internal elastic lamina and media of arteries → vascular stiffening without obstruction. "Pipestem" appearance on x-ray C. Does not obstruct blood flow; intima not involved. |

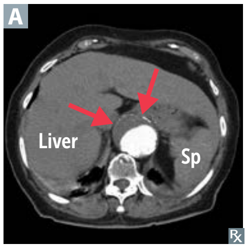


| | |
|---|---|
| **Atherosclerosis** | Very common. Disease of elastic arteries and large- and medium-sized muscular arteries; a form of arteriosclerosis caused by buildup of cholesterol plaques in intima. |
| LOCATION | Abdominal aorta > coronary artery > popliteal artery > carotid artery > circle of Willis.<br>A copy cat named Willis. |
| RISK FACTORS | Modifiable: hypertension, tobacco smoking, dyslipidemia (↑ LDL, ↓ HDL), diabetes.<br>Non-modifiable: age, male sex, postmenopausal status, family history. |
| SYMPTOMS | Angina, claudication, but can be asymptomatic. |
| PROGRESSION | Inflammation important in pathogenesis: endothelial cell dysfunction → macrophage and LDL accumulation → foam cell formation → fatty streaks → smooth muscle cell migration (involves PDGF and FGF), proliferation, and extracellular matrix deposition → fibrous plaque → complex atheromas A → calcification (calcium content correlates with risk of complications). |
| COMPLICATIONS | Aneurysms, ischemia, infarcts, peripheral vascular disease, thrombus, emboli. |




| | |
|---|---|
| **Aortic aneurysm** | Localized pathologic dilation of the aorta. May cause abdominal and/or back pain, which is a sign of leaking, dissection, or imminent rupture. |
| **Abdominal aortic aneurysm** | Usually associated with atherosclerosis. Risk factors include history of tobacco use, ↑ age, male sex, family history. May present as palpable pulsatile abdominal mass (arrows in A point to outer dilated calcified aortic wall, with partial crescent-shaped nonopacification of aorta due to flap/clot). Most often infrarenal (distal to origin of renal arteries). |




| | |
|---|---|
| **Thoracic aortic aneurysm** | Associated with cystic medial degeneration. Risk factors include hypertension, bicuspid aortic valve, connective tissue disease (eg, Marfan syndrome). Also associated with 3° syphilis (obliterative endarteritis of the vasa vasorum). Aortic root dilatation may lead to aortic valve regurgitation. |

**Traumatic aortic rupture**

Due to trauma and/or deceleration injury, most commonly at aortic isthmus (proximal descending aorta just distal to origin of left subclavian artery). X-ray may reveal widened mediastinum.

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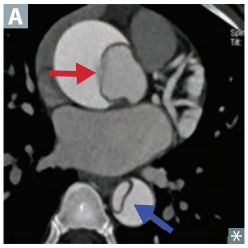
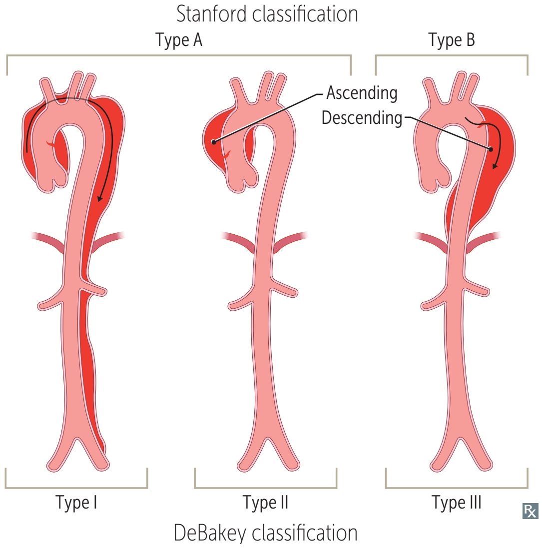
**Aortic dissection**




Longitudinal intimal tear forming a false lumen. Associated with hypertension, bicuspid aortic valve, inherited connective tissue disorders (eg, Marfan syndrome). Can present with tearing, sudden-onset chest pain radiating to the back +/– markedly unequal BP in arms. CXR can show mediastinal widening. Can result in organ ischemia, aortic rupture, death.

Stanford type **A** (proximal): involves **A**scending aorta (red arrow in A). May extend to aortic arch or descending aorta (blue arrow in A). May result in acute aortic regurgitation or cardiac tamponade. Treatment: surgery.

Stanford type **B** (distal): involves only descending aorta (**B**elow left subclavian artery). Treatment: β-blockers, then vasodilators.

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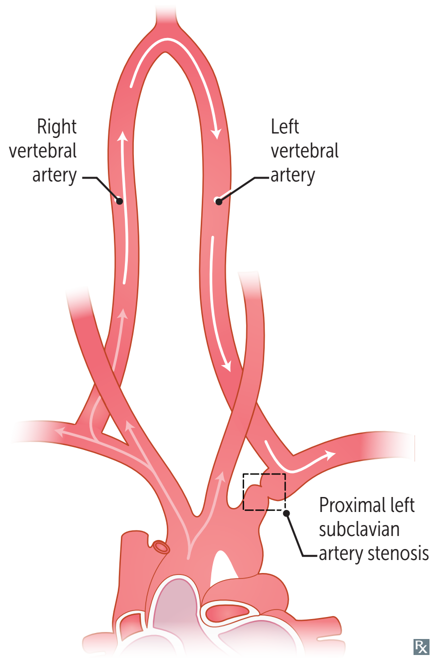
**Subclavian steal syndrome**

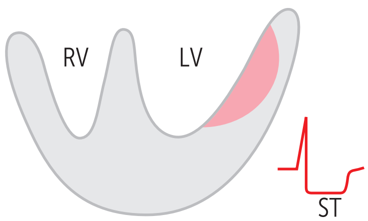
Stenosis of subclavian artery proximal to origin of vertebral artery → hypoperfusion distal to stenosis → reversed blood flow in ipsilateral vertebral artery → reduced cerebral perfusion on exertion of affected arm. Causes arm ischemia, pain, paresthesia, vertebrobasilar insufficiency (dizziness, vertigo). >15 mm Hg difference in systolic BP between arms. Associated with arteriosclerosis, Takayasu arteritis, heart surgery.

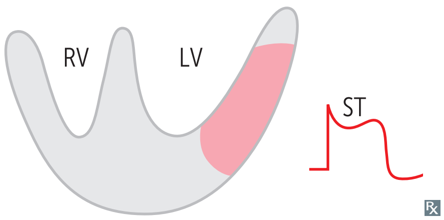


## Ischemic heart disease manifestations

| | |
|---|---|
| **Angina** | Chest pain due to ischemic myocardium 2° to coronary artery narrowing or spasm; no necrosis.<br>▪ Stable—usually 2° to atherosclerosis (≥ 70% occlusion); exertional chest pain in classic distribution (usually with ST depression on ECG), resolving with rest or nitroglycerin.<br>▪ Vasospastic (also called Prinzmetal or Variant)—occurs at rest 2° to coronary artery spasm; transient ST elevation on ECG. Tobacco smoking is a risk factor; hypertension and hypercholesterolemia are not. Triggers include cocaine, alcohol, and triptans. Treat with $Ca^{2+}$ channel blockers, nitrates, and smoking cessation (if applicable).<br>▪ Unstable—thrombosis with incomplete coronary artery occlusion; +/– ST depression and/or T-wave inversion on ECG but no cardiac biomarker elevation (unlike NSTEMI); ↑ in frequency or intensity of chest pain or any chest pain at rest. |
| **Coronary steal syndrome** | Distal to coronary stenosis, vessels are maximally dilated at baseline. Administration of vasodilators (eg, dipyridamole, regadenoson) dilates normal vessels → blood is shunted toward well-perfused areas → ischemia in myocardium perfused by stenosed vessels. Principle behind pharmacologic stress tests with coronary vasodilators. |
| **Sudden cardiac death** | Death occurs within 1 hour of symptoms, most commonly due to lethal arrhythmia (eg, ventricular fibrillation). Associated with CAD (up to 70% of cases), cardiomyopathy (hypertrophic, dilated), and hereditary ion channelopathies (eg, long QT syndrome, Brugada syndrome). Prevent with ICD. |
| **Chronic ischemic heart disease** | Progressive onset of HF over many years due to chronic ischemic myocardial damage.<br>Myocardial hibernation—potentially reversible LV systolic dysfunction in the setting of chronic ischemia. Contrast with myocardial stunning, a transient LV systolic dysfunction after a brief episode of acute ischemia. |
| **Myocardial infarction** | Most often due to rupture of coronary artery atherosclerotic plaque → acute thrombosis. ↑ cardiac biomarkers (CK-MB, troponins) are diagnostic. |

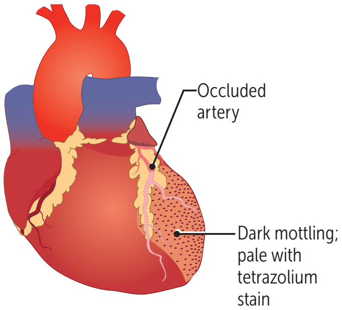
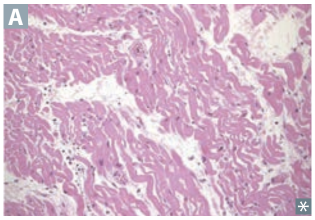
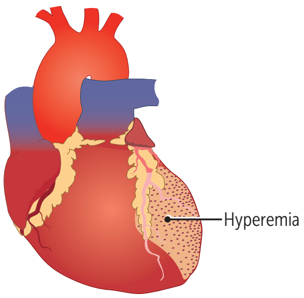
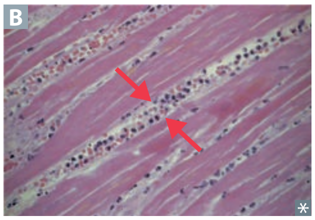
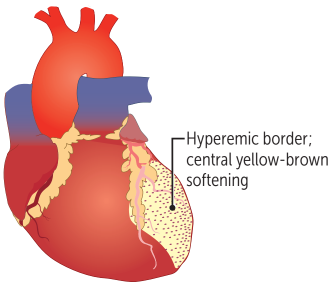
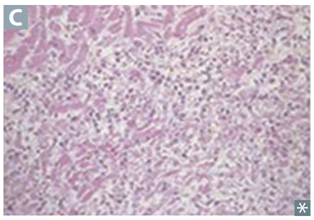
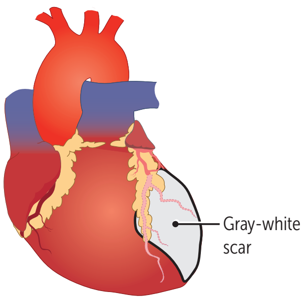
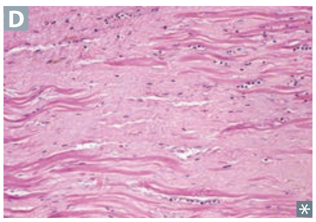
| Non–ST-segment elevation MI (NSTEMI) | ST-segment elevation MI (STEMI) |
|---|---|
| Subendocardial infarcts | Transmural infarcts |
| Subendocardium (inner 1/3) especially vulnerable to ischemia | Full thickness of myocardial wall involved |
| ST depression on ECG | ST elevation, pathologic Q waves on ECG |



## Evolution of myocardial infarction

Commonly occluded coronary arteries: LAD > RCA > circumflex.
Symptoms: diaphoresis, nausea, vomiting, severe retrosternal pain, pain in left arm and/or jaw, shortness of breath, fatigue.

| TIME | GROSS | LIGHT MICROSCOPE | COMPLICATIONS |
|---|---|---|---|
| 0–24 hours |   | Wavy fibers (0–4 hr), early coagulative necrosis (4–24 hr) A → cell content released into blood; edema, hemorrhage<br>Reperfusion injury → free radicals and ↑ $Ca^{2+}$ influx → hypercontraction of myofibrils (dark eosinophilic stripes)<br>A  | Ventricular arrhythmia, HF, cardiogenic shock |
| 1–3 days |   | Extensive coagulative necrosis<br>Tissue surrounding infarct shows acute inflammation with neutrophils B<br>B  | Postinfarction fibrinous pericarditis |
| 3–14 days |   | Macrophages, then granulation tissue at margins C<br>C  | Free wall rupture → tamponade; papillary muscle rupture → mitral regurgitation; interventricular septal rupture due to macrophage-mediated structural degradation → left-to-right shunt<br>LV pseudoaneurysm (risk of rupture) |
| 2 weeks to several months |   | Contracted scar complete D<br>D  | Dressler syndrome, HF, arrhythmias, true ventricular aneurysm (risk of mural thrombus) |

**Diagnosis of myocardial infarction**

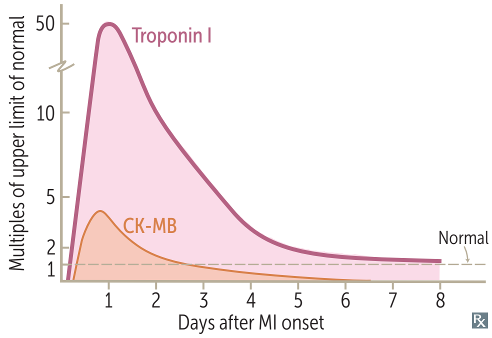
In the first 6 hours, ECG is the gold standard.

Cardiac troponin I rises after 4 hours (peaks at 24 hr) and is ↑ for 7–10 days; more specific than other protein markers.

CK-MB rises after 6–12 hours (peaks at 16–24 hr) and is predominantly found in myocardium but can also be released from skeletal muscle. Useful in diagnosing reinfarction following acute MI because levels return to normal after 48 hours.

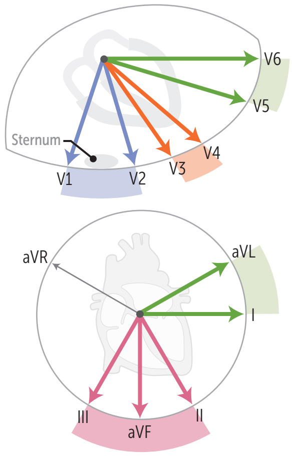
Large MIs lead to greater elevations in troponin I and CK-MB. Exact curves vary with testing procedure.

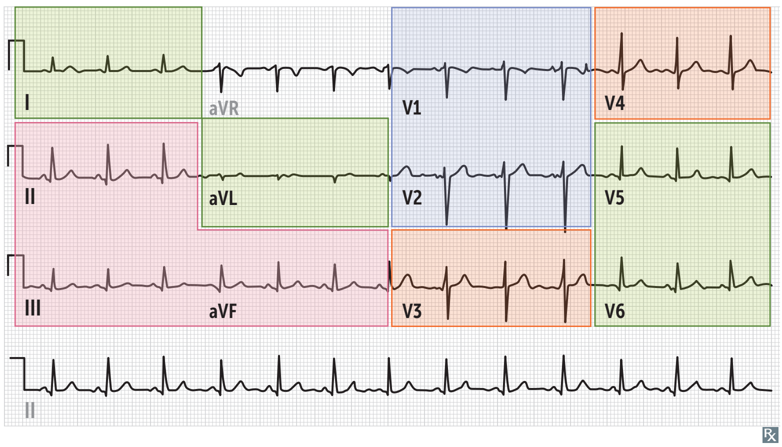
ECG changes can include ST elevation (STEMI, transmural infarct), ST depression (NSTEMI, subendocardial infarct), hyperacute (peaked) T waves, T-wave inversion, new left bundle branch block, and pathologic Q waves or poor R wave progression (evolving or old transmural infarct).




**ECG localization of STEMI**

| INFARCT LOCATION | LEADS WITH ST-SEGMENT ELEVATIONS OR Q WAVES |
|---|---|
| Anteroseptal (LAD) | $V_1$–$V_2$ |
| Anteroapical (distal LAD) | $V_3$–$V_4$ |
| Anterolateral (LAD or LCX) | $V_5$–$V_6$ |
| Lateral (LCX) | I, aVL |
| InFerior (RCA) | II, III, aVF |
| Posterior (PDA) | $V_7$–$V_9$, ST depression in $V_1$–$V_3$ with tall R waves |



**Paroxysmal supraventricular tachycardia**

A narrow QRS complex tachycardia. Most often due to atrioventricular nodal reentrant tachycardia. Commonly presents with sudden-onset palpitations, diaphoresis, lightheadedness. Treatment: terminate re-entry by slowing AV node conduction (eg, vagal maneuvers, IV adenosine). Electrical cardioversion if hemodynamically unstable. Definitive treatment is catheter ablation of re-entry tract.

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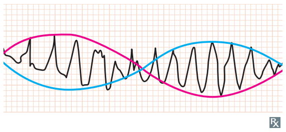
**Torsades de pointes**



Polymorphic ventricular tachycardia, characterized by shifting sinusoidal waveforms on ECG; can progress to ventricular fibrillation. Long QT interval predisposes to torsades de pointes. Caused by drugs, ↓ $K^+$, ↓ $Mg^{2+}$, ↓ $Ca^{2+}$, congenital abnormalities. Treatment includes magnesium sulfate.

Drug-induced long QT (**ABCDEF**):
- Anti**A**rrhythmics (class IA, III)
- Anti**B**iotics (eg, macrolides, fluoroquinolones)
- Anti"**C**"ychotics (eg, haloperidol, ziprasidone)
- Anti**D**epressants (eg, TCAs)
- Anti**E**metics (eg, ondansetron)
- Anti**F**ungals (eg, azoles)

Torsades de pointes = twisting of the points

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**Hereditary channelopathies**

Inherited mutations of cardiac ion channels → abnormal myocardial action potential → ↑ risk of ventricular tachyarrhythmias and sudden cardiac death (SCD).

**Brugada syndrome**

Autosomal dominant; most commonly due to loss of function mutation of $Na^+$ channels. ↑ prevalence in Asian males. ECG pattern of pseudo-right bundle branch block and ST-segment elevations in leads $V_1$-$V_2$. Prevent SCD with implantable cardioverter-defibrillator (ICD).

**Congenital long QT syndrome**

Most commonly due to loss of function mutation of $K^+$ channels (affects repolarization). Includes:
- Romano-Ward syndrome—autosomal dominant, pure cardiac phenotype (no deafness).
- Jervell and Lange-Nielsen syndrome—autosomal recessive, sensorineural deafness.

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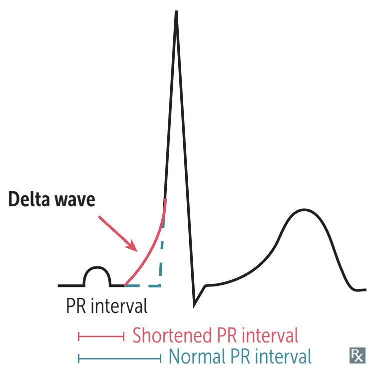
**Wolff-Parkinson-White syndrome**

Most common type of ventricular pre-excitation syndrome. Abnormal fast accessory conduction pathway from atria to ventricle (bundle of Kent) bypasses the rate-slowing AV node → ventricles begin to partially depolarize earlier → characteristic delta wave with widened QRS complex and shortened PR interval on ECG. May result in reentry circuit → supraventricular tachycardia.



## ECG tracings

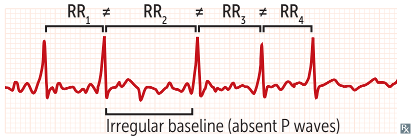
If the R is far from P, then you have a first degree.
Longer, longer, longer, drop! Then you have a Wenckebach.
If some P's don't get through, then you have a Mobitz II.
If P's and Q's don't agree, then you have a third degree.

RHYTHM | DESCRIPTION | EXAMPLE

### Atrial fibrillation

Chaotic and erratic baseline with no discrete P waves in between irregularly spaced QRS complexes. Irregularly irregular heartbeat. Most common risk factors include hypertension and coronary artery disease (CAD). Occasionally seen after episodes of excessive alcohol consumption ("holiday heart syndrome"). Can lead to thromboembolic events, particularly stroke.

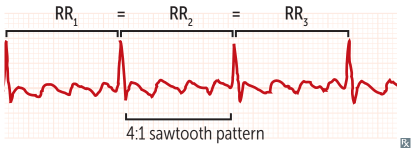
Treatment: anticoagulation, rate and rhythm control, cardioversion. Definitive treatment is catheter ablation.




### Atrial flutter

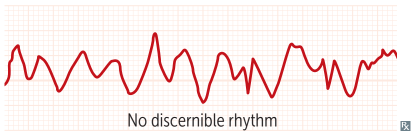
A rapid succession of identical, back-to-back atrial depolarization waves. The identical appearance accounts for the "sawtooth" appearance of the flutter waves.

Treat like atrial fibrillation +/– catheter ablation of region between tricuspid annulus and IVC.




### Ventricular fibrillation

A completely erratic rhythm with no identifiable waves. Fatal arrhythmia without immediate CPR and defibrillation.




## AV block

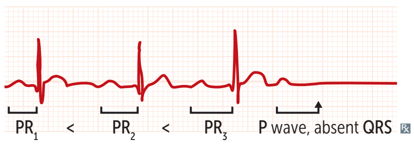
### First-degree AV block

The PR interval is prolonged (> 200 msec). Benign and asymptomatic. No treatment required.


### Second-degree AV block

#### Mobitz type I (Wenckebach)

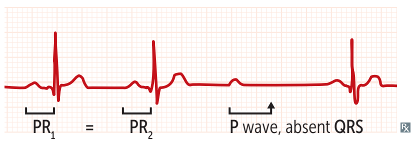
Progressive lengthening of PR interval until a beat is "dropped" (a P wave not followed by a QRS complex). Usually asymptomatic. Variable RR interval with a pattern (regularly irregular).




#### Mobitz type II

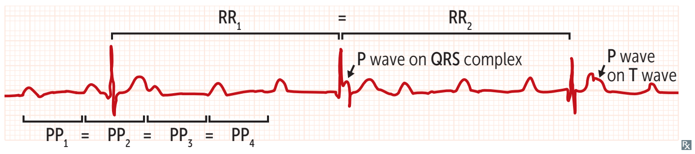
Dropped beats that are not preceded by a change in the length of the PR interval (as in type I).

May progress to 3rd-degree block. Often treated with pacemaker.



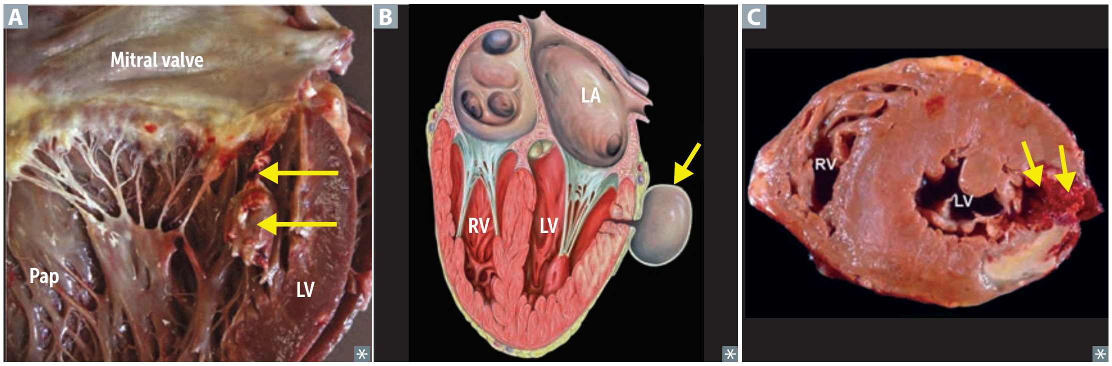

### Third-degree (complete) AV block

The atria and ventricles beat independently of each other. P waves and QRS complexes not rhythmically associated. Atrial rate > ventricular rate. Usually treated with pacemaker. Can be caused by Lym3 disease.



### Myocardial infarction complications

| | |
|---|---|
| **Cardiac arrhythmia** | Occurs within the first few days after MI. Important cause of death before reaching the hospital and within the first 24 hours post-MI. |
| **Postinfarction fibrinous pericarditis** | 1–3 days: friction rub. |
| **Papillary muscle rupture** | 2–7 days: posteromedial papillary muscle rupture A ↑ risk due to single blood supply from posterior descending artery. Can result in severe mitral regurgitation. |
| **Interventricular septal rupture** | 3–5 days: macrophage-mediated degradation → VSD → ↑ $O_2$ saturation and pressure in RV. |
| **Ventricular pseudoaneurysm formation** | 3–14 days: free wall rupture contained by adherent pericardium or scar tissue B; ↓ CO, risk of arrhythmia, embolus from mural thrombus. |
| **Ventricular free wall rupture** | 5–14 days: free wall rupture C → cardiac tamponade. LV hypertrophy and previous MI protect against free wall rupture. Acute form usually leads to sudden death. |
| **True ventricular aneurysm** | 2 weeks to several months: outward bulge with contraction ("dyskinesia"), associated with fibrosis. |
| **Dressler syndrome** | Several weeks: autoimmune phenomenon resulting in fibrinous pericarditis. |
| **LV failure and pulmonary edema** | Can occur 2° to LV infarction, VSD, free wall rupture, papillary muscle rupture with mitral regurgitation. |

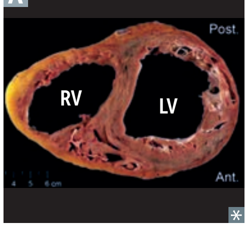
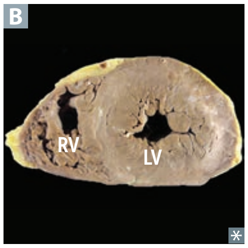



**Acute coronary syndrome treatments**

**Unstable angina/NSTEMI**—Anticoagulation (eg, heparin), antiplatelet therapy (eg, aspirin) + ADP receptor inhibitors (eg, clopidogrel), β-blockers, ACE inhibitors, statins. Symptom control with nitroglycerin +/– morphine.

**STEMI**—In addition to above, reperfusion therapy most important (percutaneous coronary intervention preferred over fibrinolysis). If RV affected (eg, RCA occlusion), support venous return/preload to maintain cardiac output (eg, IV fluids, avoiding nitroglycerin).

## Cardiomyopathies

| | | |
|---|---|---|
| **Dilated cardiomyopathy**<br>A  | Most common cardiomyopathy (90% of cases). Often idiopathic or familial (eg, due to mutation of *TTN* gene encoding the sarcomeric protein titin).<br>Other etiologies include drugs (eg, alcohol, cocaine, doxorubicin), infection (eg, coxsackie B virus, Chagas disease), ischemia (eg, CAD), systemic conditions (eg, hemochromatosis, sarcoidosis, thyrotoxicosis, wet beriberi), peripartum cardiomyopathy.<br>Findings: HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR.<br>Treatment: $Na^+$ restriction, ACE inhibitors, β-blockers, sacubitril, diuretics, mineralocorticoid receptor blockers (eg, spironolactone), digoxin, ICD, heart transplant. | Leads to systolic dysfunction.<br>Dilated cardiomyopathy A displays eccentric hypertrophy (sarcomeres added in series).<br>Takotsubo cardiomyopathy: broken heart syndrome—ventricular apical ballooning likely due to increased sympathetic stimulation (eg, stressful situations). |
| **Hypertrophic cardiomyopathy**<br>B  | 60–70% of cases are familial, autosomal dominant (most commonly due to mutations in genes encoding sarcomeric proteins, such as myosin binding protein C and β-myosin heavy chain). Causes syncope during exercise and may lead to sudden death (eg, in young athletes) due to ventricular arrhythmia.<br>Findings: S4, systolic murmur. May see mitral regurgitation due to impaired mitral valve closure.<br>Treatment: cessation of high-intensity athletics, use of β-blocker or nondihydropyridine $Ca^{2+}$ channel blockers (eg, verapamil). ICD if syncope occurs. Avoid drugs that decrease preload (eg, diuretics, vasodilators). | Diastolic dysfunction ensues.<br>Marked ventricular concentric hypertrophy (sarcomeres added in parallel) B, often septal predominance. Myofibrillar disarray and fibrosis.<br>Classified as hypertrophic obstructive cardiomyopathy when outflow from LV is obstructed. Asymmetric septal hypertrophy and systolic anterior motion of mitral valve → outflow obstruction → dyspnea, possible syncope.<br>Other causes of concentric LV hypertrophy: chronic HTN, Friedreich ataxia. |
| **Restrictive/infiltrative cardiomyopathy** | **P**ostradiation fibrosis, **L**öffler endocarditis, **E**ndocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), **A**myloidosis, **S**arcoidosis, **H**emochromatosis (**PLEAS**e **H**elp!). | Diastolic dysfunction ensues. Can have low-voltage ECG despite thick myocardium (especially in amyloidosis).<br>Löffler endocarditis—associated with hypereosinophilic syndrome; histology shows eosinophilic infiltrates in myocardium. |

## Heart failure


Clinical syndrome of cardiac pump dysfunction → congestion and low perfusion. Symptoms include dyspnea, orthopnea, fatigue; signs include S3 heart sound, rales, jugular venous distention (JVD), pitting edema A.

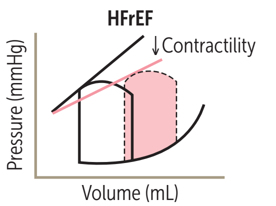
Systolic dysfunction—reduced EF, ↑ EDV; ↓ contractility often 2° to ischemia/MI or dilated cardiomyopathy.

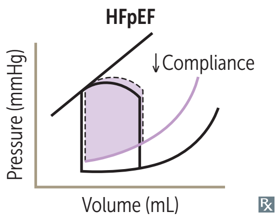
Diastolic dysfunction—preserved EF, normal EDV; ↓ compliance (↑ EDP) often 2° to myocardial hypertrophy.

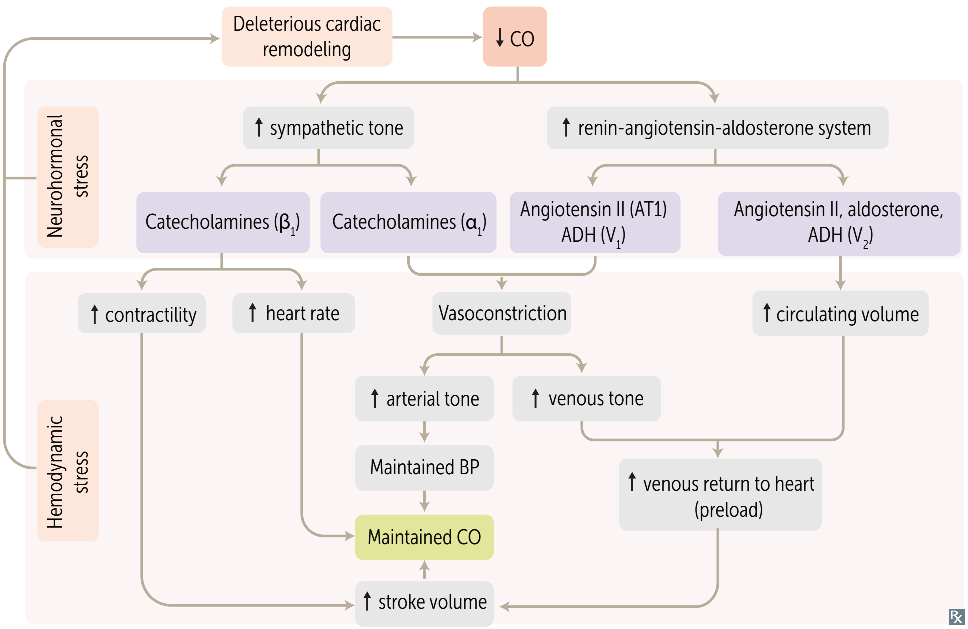
Right HF most often results from left HF. Cor pulmonale refers to isolated right HF due to pulmonary cause.

ACE inhibitors or angiotensin II receptor blockers, β-blockers (except in acute decompensated HF), and spironolactone ↓ mortality. Loop and thiazide diuretics are used mainly for symptomatic relief. Hydralazine with nitrate therapy improves both symptoms and mortality in select patients.

| Left heart failure | |
|---|---|
| **Orthopnea** | Shortness of breath when supine: ↑ venous return from redistribution of blood (immediate gravity effect) exacerbates pulmonary vascular congestion. |
| **Paroxysmal nocturnal dyspnea** | Breathless awakening from sleep: ↑ venous return from redistribution of blood, reabsorption of peripheral edema, etc. |
| **Pulmonary edema** | ↑ pulmonary venous pressure → pulmonary venous distention and transudation of fluid. Presence of hemosiderin-laden macrophages ("HF" cells) in lungs. |
| **Right heart failure** | |
| **Hepatomegaly** | ↑ central venous pressure → ↑ resistance to portal flow. Rarely, leads to "cardiac cirrhosis." Associated with nutmeg liver (mottled appearance) on gross exam. |
| **Jugular venous distention** | ↑ venous pressure. |
| **Peripheral edema** | ↑ venous pressure → fluid transudation. |



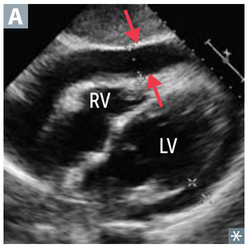



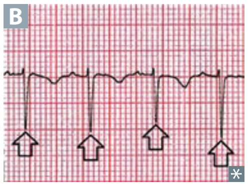
**Shock**

Inadequate organ perfusion and delivery of nutrients necessary for normal tissue and cellular function. Initially may be reversible but life threatening if not treated promptly.

<table>
<tr><th></th><th>CAUSED BY</th><th>SKIN</th><th>PCWP (PRELOAD)</th><th>CO</th><th>SVR (AFTERLOAD)</th><th>TREATMENT</th></tr>
<tr><td>Hypovolemic shock</td><td>Hemorrhage, dehydration, burns</td><td>Cold, clammy</td><td>↓↓</td><td>↓</td><td>↑</td><td>IV fluids</td></tr>
<tr><td>Cardiogenic shock</td><td>Acute MI, HF, valvular dysfunction, arrhythmia</td><td rowspan="2">Cold, clammy</td><td rowspan="2">↑ or ↓</td><td rowspan="2">↓↓</td><td rowspan="2">↑</td><td>Inotropes, diuresis</td></tr>
<tr><td>Obstructive shock</td><td>Cardiac tamponade, pulmonary embolism, tension pneumothorax</td><td>Relieve obstruction</td></tr>
<tr><td>Distributive shock</td><td>Sepsis, anaphylaxis<br>CNS injury</td><td>Warm<br>Dry</td><td>↓<br>↓</td><td>↑<br>↓</td><td>↓↓<br>↓↓</td><td>IV fluids, pressors, epinephrine (anaphylaxis)</td></tr>
</table>

**Cardiac tamponade**




Compression of the heart by fluid (eg, blood, effusions [arrows in A] in pericardial space) → ↓ CO. Equilibration of diastolic pressures in all 4 chambers.

Findings: Beck triad (hypotension, distended neck veins, distant heart sounds), ↑ HR, pulsus paradoxus. ECG shows low-voltage QRS and electrical alternans B (due to "swinging" movement of heart in large effusion).

Treatment: pericardiocentesis or surgical drainage.

**Pulsus paradoxus**—↓ in amplitude of systolic BP by > 10 mm Hg during inspiration. Seen in constrictive pericarditis, obstructive pulmonary disease (eg, Croup, OSA, Asthma, COPD), cardiac Tamponade (pea COAT).

**Bacterial endocarditis**

Acute—*S aureus* (high virulence). Large vegetations on previously normal valves A. Rapid onset.

Subacute—viridans streptococci (low virulence). Smaller vegetations on congenitally abnormal or diseased valves. Sequela of dental procedures. Gradual onset.

Symptoms: fever (most common), new murmur, **R**oth spots (**R**ound white spots on **R**etina surrounded by hemorrhage B), **O**sler nodes (**O**uchy raised lesions on finger or toe pads C due to immune complex deposition), Janeway lesions (small, painless, erythematous lesions on palm or sole) D, splinter hemorrhages E on nail bed.

Associated with glomerulonephritis, septic arterial or pulmonary emboli.

May be nonbacterial (marantic/thrombotic) 2° to malignancy, hypercoagulable state, or lupus.

**FROM JANE** with ♥:
- **F**ever
- **R**oth spots
- **O**sler nodes
- **M**urmur
- **J**aneway lesions
- **A**nemia
- **N**ail-bed hemorrhage
- **E**mboli

Requires multiple blood cultures for diagnosis.

If culture ⊖, most likely *Coxiella burnetii*, *Bartonella* spp.

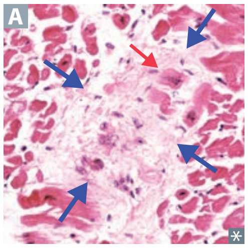
Mitral valve is most frequently involved.

**Tri**cuspid valve endocarditis is associated with IV **drug** use (don't "**tri**" **drugs**). Associated with *S aureus*, *Pseudomonas*, and *Candida*.

*S bovis (gallolyticus)* is present in colon cancer, *S epidermidis* on prosthetic valves.

Native valve endocarditis may be due to **HACEK** organisms (***H**aemophilus*, ***A**ggregatibacter* [formerly *Actinobacillus*], ***C**ardiobacterium*, ***E**ikenella*, ***K**ingella*).

**Rheumatic fever**




A consequence of pharyngeal infection with group A β-hemolytic streptococci. Late sequelae include rheu**mat**ic heart disease, which affects heart valves—**m**itral > **a**ortic >> **t**ricuspid (high-pressure valves affected most). Early lesion is mitral valve regurgitation; late lesion is mitral stenosis.

Associated with Aschoff bodies (granuloma with giant cells [blue arrows in A]), Anitschkow cells (enlarged macrophages with ovoid, wavy, rod-like nucleus [red arrow in A]), ↑ anti-streptolysin O (ASO) and ↑ anti-DNase B titers.

Immune mediated (type II hypersensitivity); not a direct effect of bacteria. Antibodies to **M** protein cross-react with self antigens, often **m**yosin (**m**olecular **m**imicry).

Treatment/prophylaxis: penicillin.

**J♥NES** (major criteria):
- **J**oint (migratory polyarthritis)
- **♥** (carditis)
- **N**odules in skin (subcutaneous)
- **E**rythema marginatum (evanescent rash with ring margin)
- **S**ydenham chorea (involuntary irregular movements of limbs and face)

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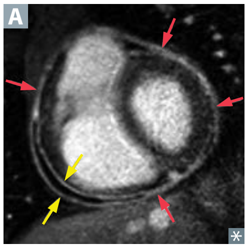
**Syphilitic heart disease**

3° syphilis disrupts the vasa vasorum of the aorta with consequent atrophy of vessel wall and dilation of aorta and valve ring.

May see calcification of aortic root, ascending aortic arch, and thoracic aorta. Leads to “tree bark” appearance of aorta.

Can result in aneurysm of ascending aorta or aortic arch, aortic insufficiency.

**Acute pericarditis**




Inflammation of the pericardium (red arrows in A). Commonly presents with sharp pain, aggravated by inspiration, and relieved by sitting up and leaning forward. Often complicated by pericardial effusion [between yellow arrows in A]. Presents with friction rub. ECG changes include widespread ST-segment elevation and/or PR depression.

Causes include idiopathic (most common; presumed viral), confirmed infection (eg, coxsackievirus B), neoplasia, autoimmune (eg, SLE, rheumatoid arthritis), uremia, cardiovascular (acute STEMI or Dressler syndrome), radiation therapy.

Treatment: NSAIDs, colchicine, glucocorticoids, dialysis (uremia).

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**Myocarditis**

Inflammation of myocardium → global enlargement of heart and dilation of all chambers. Major cause of SCD in adults < 40 years old.

Presentation highly variable, can include dyspnea, chest pain, fever, arrhythmias (persistent tachycardia out of proportion to fever is characteristic).

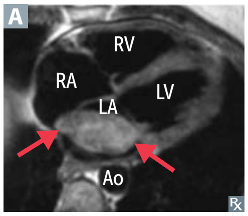
Multiple causes:

- Viral (eg, adenovirus, coxsackie B, parvovirus B19, HIV, HHV-6); lymphocytic infiltrate with focal necrosis highly indicative of viral myocarditis
- Parasitic (eg, *Trypanosoma cruzi*, *Toxoplasma gondii*)
- Bacterial (eg, *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, *Corynebacterium diphtheriae*)
- Toxins (eg, carbon monoxide, black widow venom)
- Rheumatic fever
- Drugs (eg, doxorubicin, cocaine)
- Autoimmune (eg, Kawasaki disease, sarcoidosis, SLE, polymyositis/dermatomyositis)

Complications include sudden death, arrhythmias, heart block, dilated cardiomyopathy, HF, mural thrombus with systemic emboli.

**Cardiac tumors** Most common cardiac tumor is a metastasis (eg, melanoma).

**Myxomas**




Most common 1° cardiac tumor in **adults** (arrows in A). 90% occur in the atria (mostly left atrium). Myxomas are usually described as a "ball valve" obstruction in the left atrium (associated with multiple syncopal episodes). IL-6 production by tumor → constitutional symptoms (eg, fever, weight loss). May auscultate early diastolic "tumor plop" sound. Histology: gelatinous material, myxoma cells immersed in glycosaminoglycans.

**Adults** make **6 myx**ed drinks.

**Rhabdomyomas** Most frequent 1° cardiac tumor in children (associated with tuberous sclerosis). Histology: hamartomatous growths. More common in the ventricles.

**Kussmaul sign**

Paradoxical ↑ in JVP on inspiration (normally, inspiration → negative intrathoracic pressure → ↑ venous return → ↓ JVP).

Impaired RV filling → blood backs up into vena cava → ↓ venous return as negative intrathoracic pressure is insufficient to bring blood to right heart → Kussmaul sign. May be seen with constrictive pericarditis, restrictive cardiomyopathy, right heart failure, massive pulmonary embolism, right atrial or ventricular tumors.

**Hereditary hemorrhagic telangiectasia**

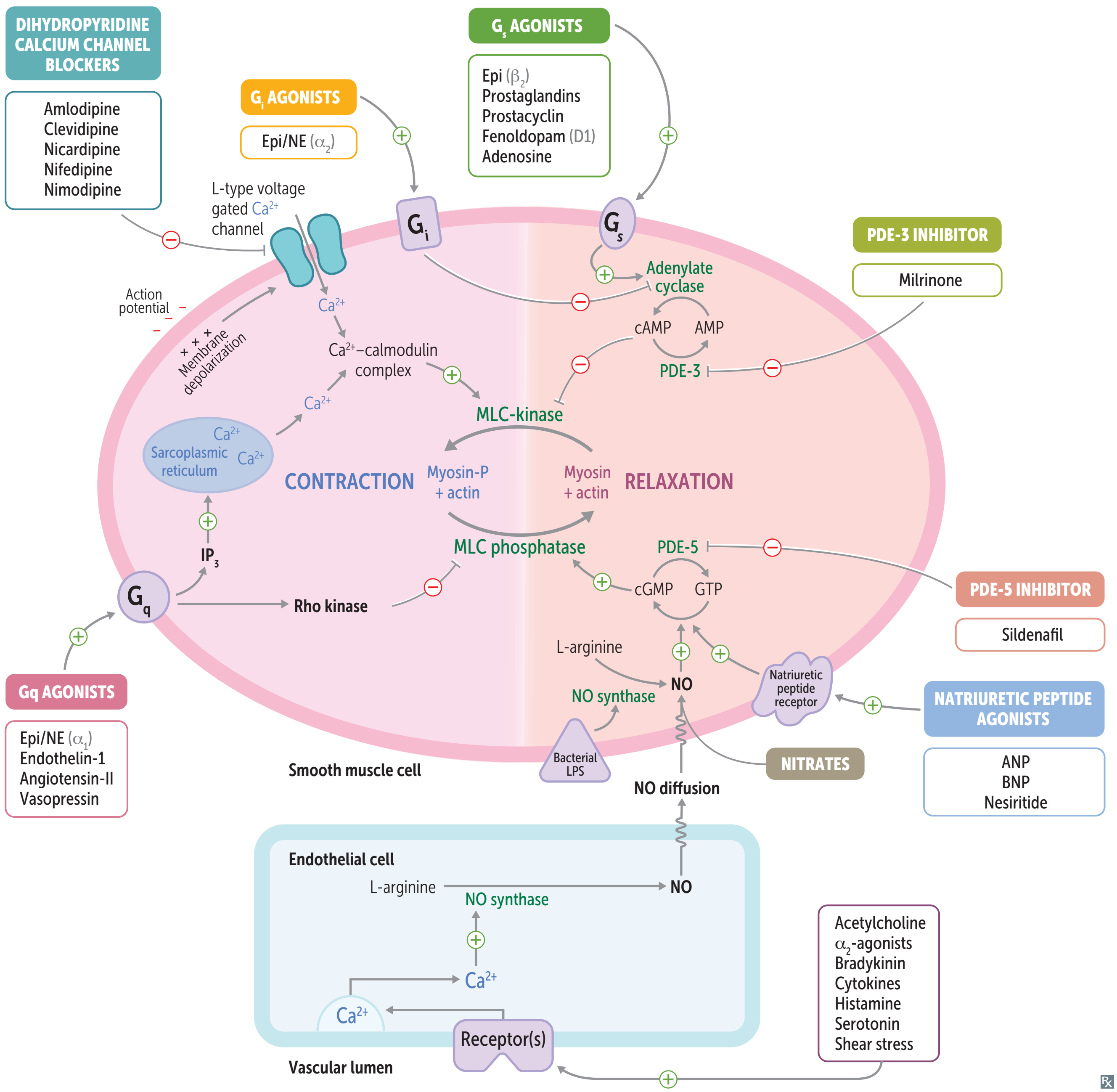
Also called Osler-Weber-Rendu syndrome. Autosomal dominant disorder of blood vessels. Findings: blanching lesions (telangiectasias) on skin and mucous membranes, recurrent epistaxis, skin discolorations, arteriovenous malformations (AVMs), GI bleeding, hematuria.

## ▸ CARDIOVASCULAR—PHARMACOLOGY

### Hypertension treatment

| | | |
|---|---|---|
| **Primary (essential) hypertension** | Thiazide diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine $Ca^{2+}$ channel blockers. | |
| **Hypertension with heart failure** | Diuretics, ACE inhibitors/ARBs, β-blockers (compensated HF), aldosterone antagonists. | β-blockers must be used cautiously in decompensated HF and are contraindicated in cardiogenic shock.<br>In HF, ARBs may be combined with the neprilysin inhibitor sacubitril. |
| **Hypertension with diabetes mellitus** | ACE inhibitors/ARBs, $Ca^{2+}$ channel blockers, thiazide diuretics, β-blockers. | ACE inhibitors/ARBs are protective against diabetic nephropathy.<br>β-blockers can mask hypoglycemia symptoms. |
| **Hypertension in asthma** | ARBs, $Ca^{2+}$ channel blockers, thiazide diuretics, cardioselective β-blockers. | Avoid nonselective β-blockers to prevent $\beta_2$-receptor–induced bronchoconstriction.<br>Avoid ACE inhibitors to prevent confusion between drug or asthma-related cough. |
| **Hypertension in pregnancy** | **N**ifedipine, **m**ethyldopa, **l**abetalol, **h**ydralazine. | **N**ew **m**oms **l**ove **h**ugs. |

### Cardiovascular agents and molecular targets



| | |
|---|---|
| **Calcium channel blockers** | Amlodipine, clevidipine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular smooth muscle); diltiazem, verapamil (nondihydropyridines, act on heart). |
| MECHANISM | Block voltage-dependent L-type calcium channels of cardiac and smooth muscle → ↓ muscle contractility.<br>Vascular smooth muscle—amlodipine = nifedipine > diltiazem > verapamil.<br>Heart—verapamil > diltiazem > amlodipine = nifedipine. |
| CLINICAL USE | Dihydropyridines (except nimodipine): hypertension, angina (including vasospastic type), Raynaud phenomenon.<br>Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm).<br>Nicardipine, clevidipine: hypertensive urgency or emergency.<br>Nondihydropyridines: hypertension, angina, atrial fibrillation/flutter. |
| ADVERSE EFFECTS | Gingival hyperplasia.<br>Dihydropyridine: peripheral edema, flushing, dizziness.<br>Nondihydropyridine: cardiac depression, AV block, hyperprolactinemia (verapamil), constipation. |

| | |
|---|---|
| **Hydralazine** | |
| MECHANISM | ↑ cGMP → smooth muscle relaxation. Vasodilates arterioles > veins; afterload reduction. |
| CLINICAL USE | Severe hypertension (particularly acute), HF (with organic nitrate). Safe to use during pregnancy. Frequently coadministered with a β-blocker to prevent reflex tachycardia. |
| ADVERSE EFFECTS | Compensatory tachycardia (contraindicated in angina/CAD), fluid retention, headache, angina, drug-induced lupus. |

| | |
|---|---|
| **Hypertensive emergency** | Treat with labetalol, clevidipine, fenoldopam, nicardipine, nitroprusside. |
| **Nitroprusside** | Short acting vasodilator (arteries = veins); ↑ cGMP via direct release of NO. Can cause cyanide toxicity (releases cyanide). |
| **Fenoldopam** | Dopamine $D_1$ receptor agonist—coronary, peripheral, renal, and splanchnic vasodilation. ↓ BP, ↑ natriuresis. Also used postoperatively as an antihypertensive. Can cause hypotension, tachycardia, flushing, headache, nausea. |

| | |
|---|---|
| **Nitrates** | Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate. |
| MECHANISM | Vasodilate by ↑ NO in vascular smooth muscle → ↑ in cGMP and smooth muscle relaxation. Dilate veins >> arteries. ↓ preload. |
| CLINICAL USE | Angina, acute coronary syndrome, pulmonary edema. |
| ADVERSE EFFECTS | Reflex tachycardia (treat with β-blockers), hypotension, flushing, headache, "Monday disease" in industrial nitrate exposure: development of tolerance for the vasodilating action during the work week and loss of tolerance over the weekend → tachycardia, dizziness, headache upon reexposure. Contraindicated in right ventricular infarction, hypertrophic cardiomyopathy, and with concurrent PDE-5 inhibitor use. |

**Antianginal therapy**

Goal is reduction of myocardial $O_2$ consumption ($MVO_2$) by ↓ 1 or more of the determinants of $MVO_2$: end-diastolic volume, BP, HR, contractility.

| COMPONENT | NITRATES | β-BLOCKERS | NITRATES + β-BLOCKERS |
|---|---|---|---|
| End-diastolic volume | ↓ | No effect or ↑ | No effect or ↓ |
| Blood pressure | ↓ | ↓ | ↓ |
| Contractility | ↑ (reflex response) | ↓ | Little/no effect |
| Heart rate | ↑ (reflex response) | ↓ | No effect or ↓ |
| Ejection time | ↓ | ↑ | Little/no effect |
| $MVO_2$ | ↓ | ↓ | ↓↓ |

Verapamil is similar to β-blockers in effect.
Pindolol and acebutolol are partial β-agonists that should be used with caution in angina.

**Ranolazine**

| | |
|---|---|
| MECHANISM | Inhibits the late phase of inward sodium current thereby reducing diastolic wall tension and oxygen consumption. Does not affect heart rate or blood pressure. |
| CLINICAL USE | Refractory angina. |
| ADVERSE EFFECTS | Constipation, dizziness, headache, nausea. |

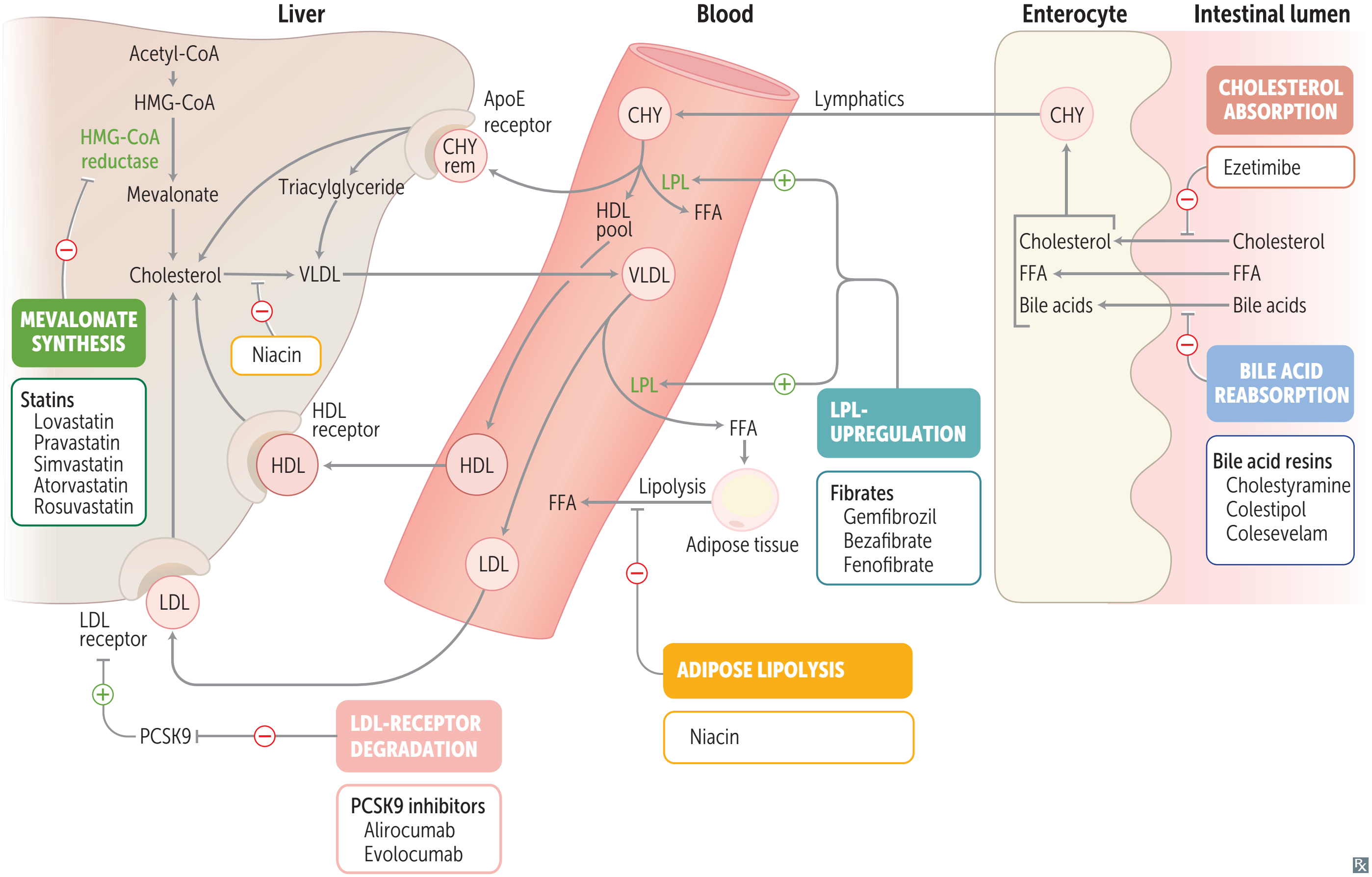
**Sacubitril**

| | |
|---|---|
| MECHANISM | A neprilysin inhibitor; prevents degradation of bradykinin, natriuretic peptides, angiotensin II, and substance P → ↑ vasodilation, ↓ ECF volume. |
| CLINICAL USE | Used in combination with valsartan (an ARB) to treat HFrEF. |
| ADVERSE EFFECTS | Hypotension, hyperkalemia, cough, dizziness; contraindicated with ACE inhibitors due to angioedema (both drugs ↑ bradykinin). |

### Lipid-lowering agents

| DRUG | LDL | HDL | TRIGLYCERIDES | MECHANISMS OF ACTION | ADVERSE EFFECTS/PROBLEMS |
|---|---|---|---|---|---|
| **HMG-CoA reductase inhibitors** Atorvastatin, simvastatin | ↓↓↓ | ↑ | ↓ | Inhibit conversion of HMG-CoA to mevalonate, a cholesterol precursor; → ↓ intrahepatic cholesterol → ↑ LDL receptor recycling → ↑ LDL catabolism<br>↓ in mortality in patients with CAD | Hepatotoxicity (↑ LFTs), myopathy (esp when used with fibrates or niacin) |
| **Bile acid resins** Cholestyramine, colestipol, colesevelam | ↓↓ | ↑ slightly | ↑ slightly | Prevent intestinal reabsorption of bile acids; liver must use cholesterol to make more | GI upset, ↓ absorption of other drugs and fat-soluble vitamins |
| **Ezetimibe** | ↓↓ | ↑/— | ↓/— | Prevents cholesterol absorption at small intestine brush border | Rare ↑ LFTs, diarrhea |
| **Fibrates** Gemfibrozil, bezafibrate, fenofibrate | ↓ | ↑ | ↓↓↓ | Activate PPAR-α → upregulate LPL → ↑ TG clearance<br>Activate PPAR-α → induce HDL synthesis | Myopathy (↑ risk with statins), cholesterol gallstones (via inhibition of cholesterol 7α-hydroxylase) |
| **Niacin** | ↓↓ | ↑↑ | ↓ | Inhibits lipolysis (hormone-sensitive lipase) in adipose tissue; reduces hepatic VLDL synthesis | Flushed face (prostaglandin mediated; ↓ by NSAIDs or long-term use)<br>Hyperglycemia<br>Hyperuricemia |
| **PCSK9 inhibitors** Alirocumab, evolocumab | ↓↓↓ | ↑ | ↓ | Inactivation of LDL-receptor degradation → ↑ removal of LDL from bloodstream | Myalgias, delirium, dementia, other neurocognitive effects |
| **Fish oil and marine omega-3 fatty acids** | ↑ slightly | ↑ slightly | ↓ at high doses | Believed to decrease FFA delivery to liver and decrease activity of TG-synthesizing enzymes | Nausea, fish-like taste |

## Lipid-lowering agents *(continued)*

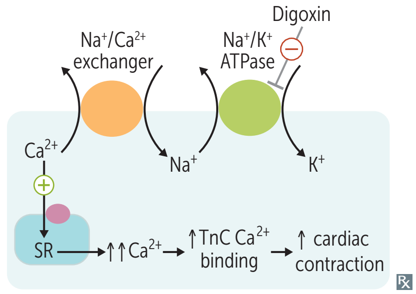



## Cardiac glycosides

Digoxin.

**MECHANISM**

Direct inhibition of $Na^+/K^+$ ATPase → indirect inhibition of $Na^+/Ca^{2+}$ exchanger. ↑ $[Ca^{2+}]_i$ → positive inotropy. Stimulates vagus nerve → ↓ HR.




**CLINICAL USE**

HF (↑ contractility); atrial fibrillation (↓ conduction at AV node and depression of SA node).

**ADVERSE EFFECTS**

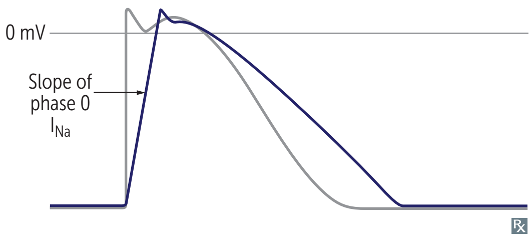
Cholinergic effects (nausea, vomiting, diarrhea), blurry **yellow** vision (think van **Glow**), arrhythmias, AV block.
Can lead to hyperkalemia, which indicates poor prognosis.
Factors predisposing to toxicity: renal failure (↓ excretion), hypokalemia (permissive for digoxin binding at $K^+$-binding site on $Na^+/K^+$ ATPase), drugs that displace digoxin from tissue-binding sites, and ↓ clearance (eg, verapamil, amiodarone, quinidine).

**ANTIDOTE**

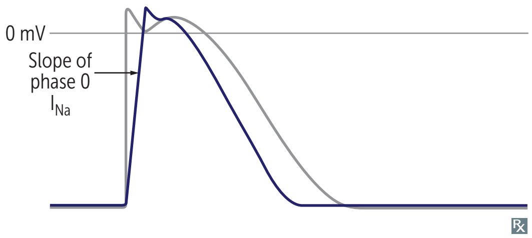
Slowly normalize $K^+$, cardiac pacer, anti-digoxin Fab fragments, $Mg^{2+}$.

| | |
|---|---|
| **Antiarrhythmics—sodium channel blockers (class I)** | Slow or block conduction (especially in depolarized cells). ↓ slope of phase 0 depolarization. ↑ action at faster HR. State dependent ↑ HR → shorter diastole, $Na^+$ channels spend less time in resting state (drugs dissociate during this state) → less time for drug to dissociate from receptor. Effect most pronounced in IC>IA>IB due to relative binding strength. Fast taxi CAB. |

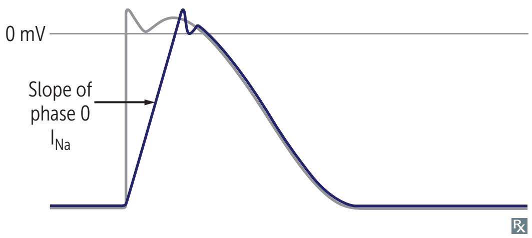
| | |
|---|---|
| **Class IA** | Quinidine, procainamide, disopyramide. “The queen proclaims Diso’s pyramid.” |
| MECHANISM | Moderate $Na^+$ channel blockade.<br>↑ AP duration, ↑ effective refractory period (ERP) in ventricular action potential, ↑ QT interval, some potassium channel blocking effects. |
| CLINICAL USE | Both atrial and ventricular arrhythmias, especially re-entrant and ectopic SVT and VT. |
| ADVERSE EFFECTS | Cinchonism (headache, tinnitus with quinidine), reversible SLE-like syndrome (procainamide), HF (disopyramide), thrombocytopenia, torsades de pointes due to ↑ QT interval. |



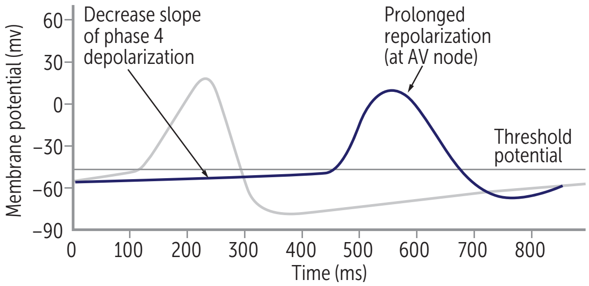

| | |
|---|---|
| **Class IB** | Lidocaine, phenytoin, mexiletine. “I’d Buy Liddy’s phine Mexican tacos.” |
| MECHANISM | Weak $Na^+$ channel blockade.<br>↓ AP duration. Preferentially affect ischemic or depolarized Purkinje and ventricular tissue. |
| CLINICAL USE | Acute ventricular arrhythmias (especially post-MI), digitalis-induced arrhythmias.<br>IB is Best post-MI. |
| ADVERSE EFFECTS | CNS stimulation/depression, cardiovascular depression. |




| | |
|---|---|
| **Class IC** | Flecainide, propafenone. “Can I have fries, please?” |
| MECHANISM | Strong $Na^+$ channel blockade.<br>Significantly prolongs ERP in AV node and accessory bypass tracts. No effect on ERP in Purkinje and ventricular tissue.<br>Minimal effect on AP duration. |
| CLINICAL USE | SVTs, including atrial fibrillation. Only as a last resort in refractory VT. |
| ADVERSE EFFECTS | Proarrhythmic, especially post-MI (contraindicated). IC is Contraindicated in structural and ischemic heart disease. |

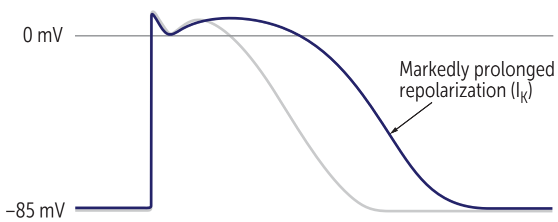


| **Antiarrhythmics—β-blockers (class II)** | Metoprolol, propranolol, esmolol, atenolol, timolol, carvedilol. |
|---|---|
| MECHANISM | Decrease SA and AV nodal activity by ↓ cAMP, ↓ $Ca^{2+}$ currents. Suppress abnormal pacemakers by ↓ slope of phase 4.<br>AV node particularly sensitive—↑ PR interval. Esmolol very short acting. |
| CLINICAL USE | SVT, ventricular rate control for atrial fibrillation and atrial flutter. |
| ADVERSE EFFECTS | Impotence, exacerbation of COPD and asthma, cardiovascular effects (bradycardia, AV block, HF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia.<br>Metoprolol can cause dyslipidemia. Propranolol can exacerbate vasospasm in vasospastic angina. β-blockers (except the nonselective α- and β-antagonists carvedilol and labetalol) cause unopposed $\alpha_1$-agonism if given alone for pheochromocytoma or for cocaine toxicity (unsubstantiated). Treat β-blocker overdose with saline, atropine, glucagon. |



Pacemaker cell action potential

| **Antiarrhythmics—potassium channel blockers (class III)** | **A**miodarone, **I**butilide, **D**ofetilide, **S**otalol. | **AIDS**. |
|---|---|---|
| MECHANISM | ↑ AP duration, ↑ ERP, ↑ QT interval. | |
| CLINICAL USE | Atrial fibrillation, atrial flutter; ventricular tachycardia (amiodarone, sotalol). | |
| ADVERSE EFFECTS | Sotalol—torsades de pointes, excessive β blockade.<br>Ibutilide—torsades de pointes.<br>Amiodarone—pulmonary fibrosis, hepatotoxicity, hypothyroidism or hyperthyroidism (am**iod**arone is 40% **iod**ine by weight), acts as hapten (corneal deposits, blue/gray skin deposits resulting in photodermatitis), neurologic effects, constipation, cardiovascular effects (bradycardia, heart block, HF). | Remember to check PFTs, LFTs, and TFTs when using amiodarone.<br>Amiodarone is lipophilic and has class I, II, III, and IV effects. |

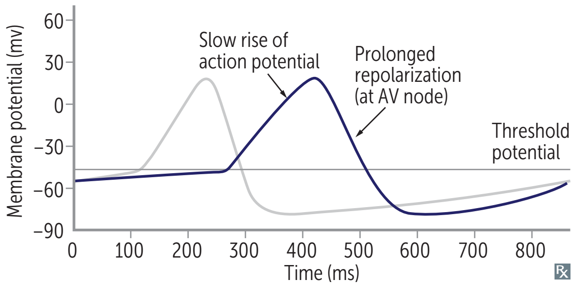


Cell action potential

## Antiarrhythmics—calcium channel blockers (class IV)

Diltiazem, verapamil.

| | |
|---|---|
| MECHANISM | Decrease conduction velocity, ↑ ERP, ↑ PR interval. |
| CLINICAL USE | Prevention of nodal arrhythmias (eg, SVT), rate control in atrial fibrillation. |
| ADVERSE EFFECTS | Constipation, flushing, edema, cardiovascular effects (HF, AV block, sinus node depression). |




## Other antiarrhythmics

| | |
|---|---|
| **Adenosine** | ↑ $K^+$ out of cells → hyperpolarizing the cell and ↓ $I_{Ca}$, decreasing AV node conduction. Drug of choice in diagnosing/terminating certain forms of SVT. Very short acting (~ 15 sec). Effects blunted by theophylline and caffeine (both are adenosine receptor antagonists). Adverse effects include flushing, hypotension, chest pain, sense of impending doom, bronchospasm. |
| **Magnesium** | Effective in torsades de pointes and digoxin toxicity. |

## Ivabradine

| | |
|---|---|
| MECHANISM | IVabradine prolongs slow depolarization (phase "IV") by selectively inhibiting "funny" sodium channels ($I_f$). |
| CLINICAL USE | Chronic stable angina in patients who cannot take β-blockers. Chronic HFrEF. |
| ADVERSE EFFECTS | Luminous phenomena/visual brightness, hypertension, bradycardia. |

# Endocrine

*"If you skew the endocrine system, you lose the pathways to self."*

—Hilary Mantel

*"Sometimes you need a little crisis to get your adrenaline flowing and help you realize your potential."*

—Jeannette Walls, *The Glass Castle*

*"Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy."*

—Elaine Sherman, *Book of Divine Indulgences*

The endocrine system comprises widely distributed organs that work in a highly integrated manner to orchestrate a state of hormonal equilibrium within the body. Generally speaking, endocrine diseases can be classified either as diseases of underproduction or overproduction, or as conditions involving the development of mass lesions—which themselves may be associated with underproduction or overproduction of hormones. Therefore, study the endocrine system first by learning the glands, their hormones, and their regulation, and then by integrating disease manifestations with diagnosis and management. Take time to learn the multisystem connections.

## ▶ ENDOCRINE—EMBRYOLOGY

### Thyroid development

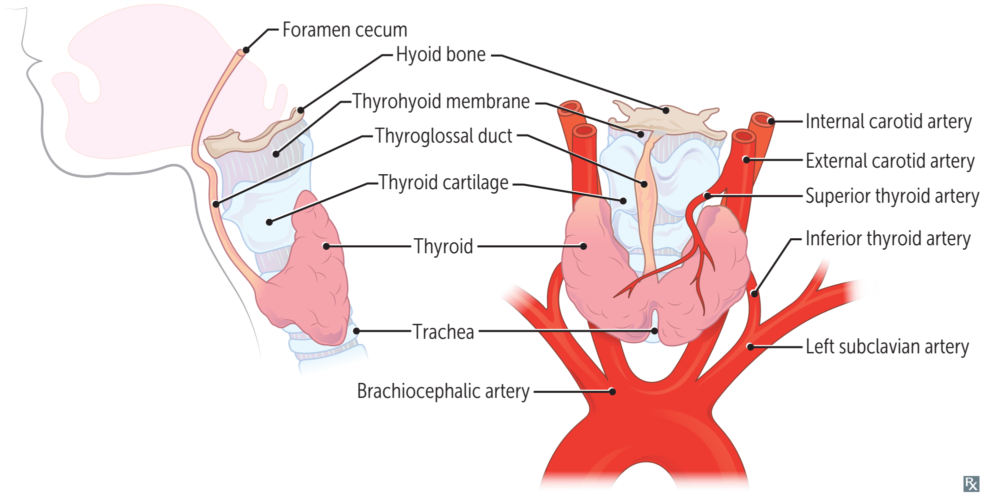

Thyroid diverticulum arises from floor of primitive pharynx and descends into neck. Connected to tongue by thyroglossal duct, which normally disappears but may persist as cysts or the pyramidal lobe of thyroid. Foramen cecum is normal remnant of thyroglossal duct.

Most common ectopic thyroid tissue site is the tongue (lingual thyroid). Removal may result in hypothyroidism if it is the only thyroid tissue present.

Thyroglossal duct cyst A presents as an anterior midline neck mass that moves with swallowing or protrusion of the tongue (vs persistent cervical sinus leading to pharyngeal cleft cyst in lateral neck).

Thyroid follicular cells derived from endoderm.

Parafollicular cells arise from 4th pharyngeal pouch.



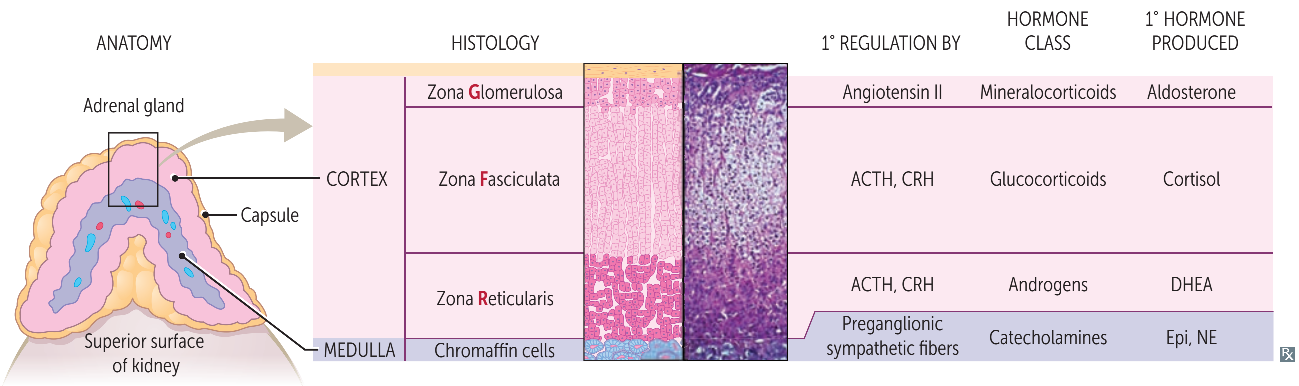
## ▶ ENDOCRINE—ANATOMY

### Pituitary gland

| | | |
|---|---|---|
| **Anterior pituitary (adenohypophysis)** | Secretes FSH, LH, ACTH, TSH, prolactin, GH, and β-endorphin. Melanotropin (MSH) secreted from intermediate lobe of pituitary. Derived from oral ectoderm (Rathke pouch).<br>▪ α subunit—hormone subunit common to TSH, LH, FSH, and hCG.<br>▪ β subunit—determines hormone specificity. | **Pro**opiomelanocortin derivatives—**β**-endorphin, **A**CTH, and **M**SH. Go **pro** with a **BAM**!<br>**FLAT PiG**: **F**SH, **L**H, **A**CTH, **T**SH, **P**RL, **G**H.<br>**B-FLAT**: **B**asophils—**F**SH, **L**H, **A**CTH, **T**SH.<br>**Acid PiG**: **Acid**ophils — **P**RL, **G**H. |
| **Posterior pituitary (neurohypophysis)** | Stores and releases vasopressin (antidiuretic hormone, or ADH) and oxytocin, both made in the hypothalamus (supraoptic and paraventricular nuclei) and transported to posterior pituitary via neurophysins (carrier proteins). Derived from **neuro**ectoderm. | |

### Adrenal cortex and medulla

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).

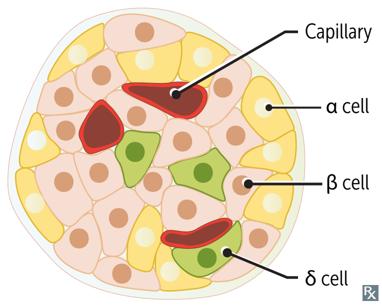



**GFR** corresponds with **s**alt (mineralocorticoids), **s**ugar (glucocorticoids), and **s**ex (androgens). "The deeper you go, the sweeter it gets."

### Endocrine pancreas cell types

Islets of Langerhans are collections of α, β, and δ endocrine cells. Islets arise from pancreatic buds.

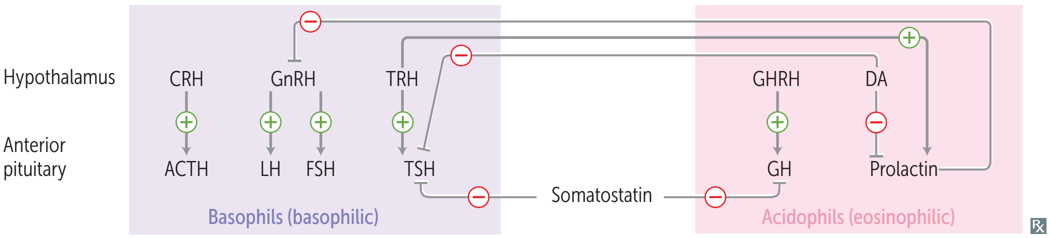
α = gluc**α**gon (peripheral)
β = insulin (central)
δ = somatostatin (interspersed)



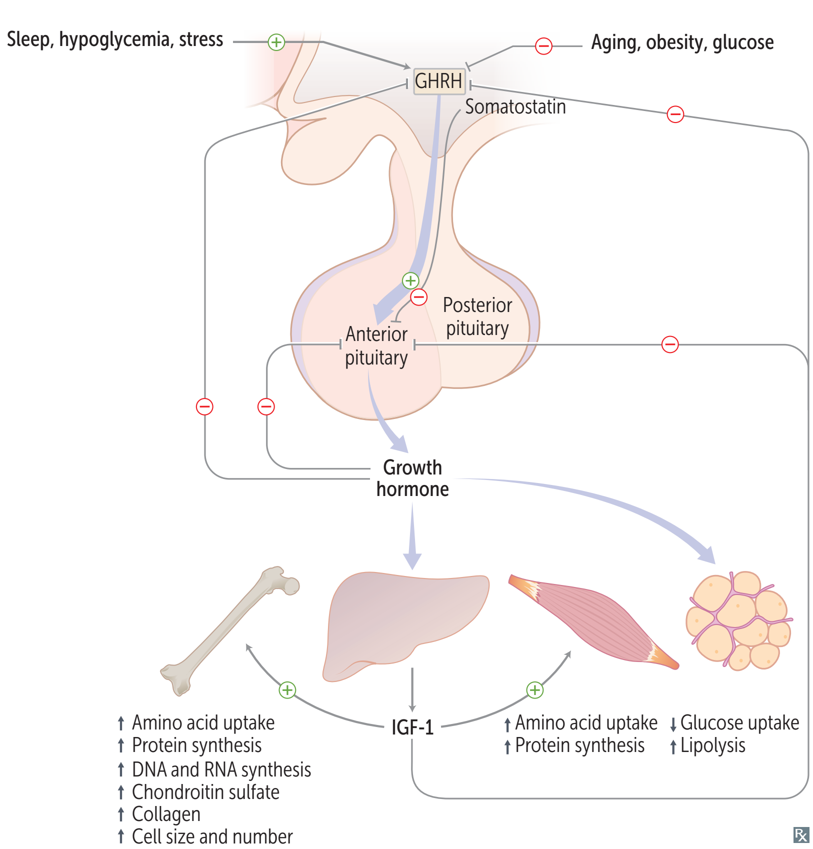
## ▸ ENDOCRINE—PHYSIOLOGY

### Hypothalamic-pituitary hormones

| HORMONE | FUNCTION | CLINICAL NOTES |
|---|---|---|
| **ADH** | ↑ water permeability of distal convoluted tubule and collecting duct cells in kidney to ↑ water reabsorption | Stimulus for secretion is ↑ plasma osmolality, except in SIADH, in which ADH is elevated despite ↓ plasma osmolality |
| **CRH** | ↑ ACTH, MSH, β-endorphin | ↓ in chronic exogenous steroid use |
| **Dopamine** | ↓ prolactin, TSH | Also called prolactin-inhibiting factor<br>Dopamine antagonists (eg, antipsychotics) can cause galactorrhea due to hyperprolactinemia |
| **GHRH** | ↑ GH | Analog (tesamorelin) used to treat HIV-associated lipodystrophy |
| **GnRH** | ↑ FSH, LH | Suppressed by hyperprolactinemia<br>Tonic GnRH analog (eg, leuprolide) suppresses hypothalamic–pituitary–gonadal axis.<br>Pulsatile GnRH leads to puberty, fertility |
| **MSH** | ↑ melanogenesis by melanocytes | Causes hyperpigmentation in Cushing disease, as MSH and ACTH share the same precursor molecule, proopiomelanocortin |
| **Oxytocin** | Causes uterine contractions during labor.<br>Responsible for milk letdown reflex in response to suckling. | Modulates fear, anxiety, social bonding, mood, and depression |
| **Prolactin** | ↓ GnRH<br>Stimulates lactogenesis. | Pituitary prolactinoma → amenorrhea, osteoporosis, hypogonadism, galactorrhea<br>Breastfeeding → ↑ prolactin → ↓ GnRH → delayed postpartum ovulation (natural contraception) |
| **Somatostatin** | ↓ GH, TSH | Also called growth hormone inhibiting hormone (GHIH)<br>Analogs used to treat acromegaly |
| **TRH** | ↑ TSH, prolactin | ↑ TRH (eg, in 1°/2° hypothyroidism) may increase prolactin secretion → galactorrhea |



## Growth hormone




Also called somatotropin. Secreted by anterior pituitary.
Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion by liver. ↑ insulin resistance (diabetogenic).
Released in pulses in response to growth hormone–releasing hormone (GHRH).
Secretion ↑ during exercise, deep sleep, puberty, hypoglycemia.
Secretion ↓ by glucose, somatostatin, somatomedin (regulatory molecule secreted by liver in response to GH acting on target tissues).
Excess secretion of GH (eg, pituitary adenoma) may cause acromegaly (adults) or gigantism (children). Treatment: somatostatin analogs (eg, octreotide) or surgery.

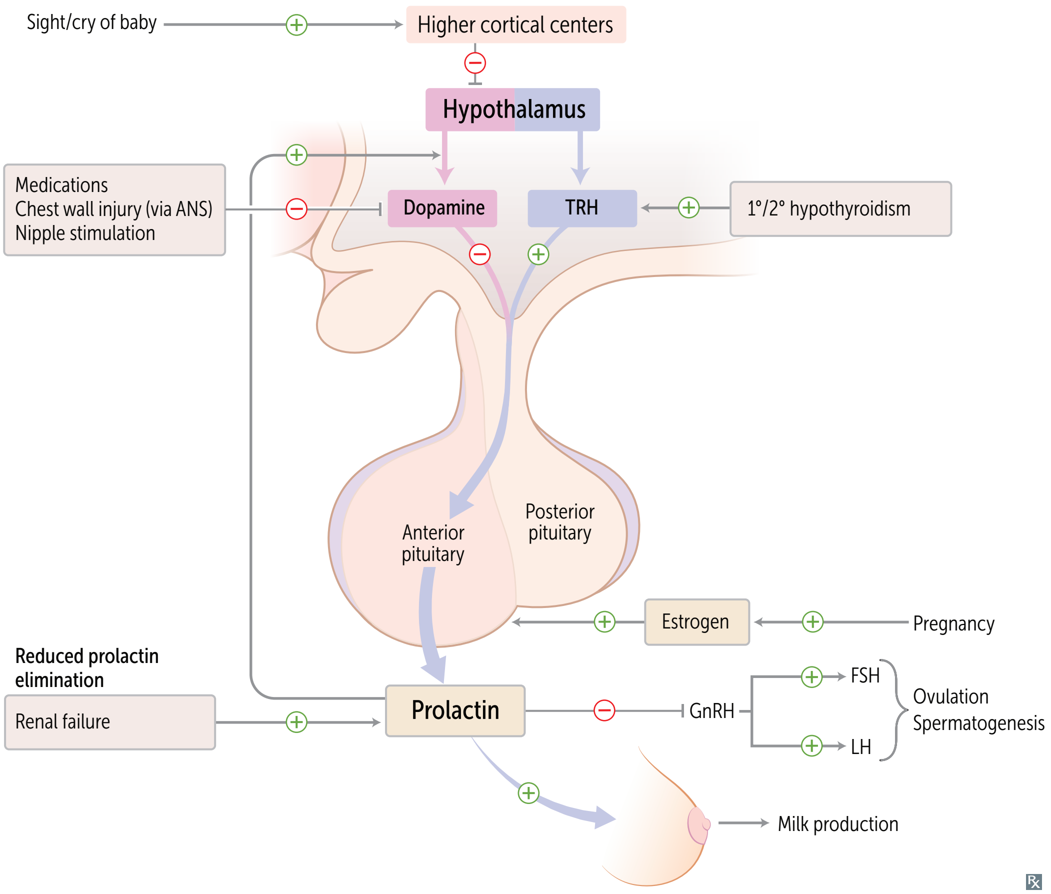
## Antidiuretic hormone

Also called vasopressin.

| | | |
|---|---|---|
| SOURCE | Synthesized in hypothalamus (supraoptic and paraventricular nuclei), stored and secreted by posterior pituitary. | |
| FUNCTION | Regulates blood pressure ($V_1$-receptors) and serum osmolality ($V_2$-receptors). Primary function is serum osmolality regulation (ADH ↓ serum osmolality, ↑ urine osmolality) via regulation of aquaporin channel insertion in principal cells of renal collecting duct. | ADH level is ↓ in central diabetes insipidus (DI), normal or ↑ in nephrogenic DI. Nephrogenic DI can be caused by mutation in $V_2$-receptor. Desmopressin (ADH analog) is a treatment for central DI and nocturnal enuresis. |
| REGULATION | Plasma osmolality (1°); hypovolemia. | |

## Prolactin

| | | |
|---|---|---|
| SOURCE | Secreted mainly by anterior pituitary. | Structurally homologous to growth hormone. |
| FUNCTION | Stimulates milk production in breast; inhibits ovulation in females and spermatogenesis in males by inhibiting GnRH synthesis and release. | Excessive amounts of prolactin associated with ↓ libido. |
| REGULATION | Prolactin secretion from anterior pituitary is tonically inhibited by dopamine from tuberoinfundibular pathway of hypothalamus. Prolactin in turn inhibits its own secretion by ↑ dopamine synthesis and secretion from hypothalamus. TRH ↑ prolactin secretion (eg, in 1° or 2° hypothyroidism). | Dopamine agonists (eg, bromocriptine) inhibit prolactin secretion and can be used in treatment of prolactinoma.<br>Dopamine antagonists (eg, most antipsychotics, metoclopramide) and estrogens (eg, OCPs, pregnancy) stimulate prolactin secretion. |



## Thyroid hormones

Thyroid produces triiodothyronine ($T_3$) and thyroxine ($T_4$), iodine-containing hormones that control the body's metabolic rate.

**SOURCE**

Follicles of thyroid. 5′-deiodinase converts $T_4$ (the major thyroid product) to $T_3$ in peripheral tissue (5, 4, 3). Peripheral conversion is inhibited by glucocorticoids, β-blockers, and propylthiouracil (PTU). Reverse $T_3$ ($rT_3$) is a metabolically inactive byproduct of the peripheral conversion of $T_4$ and its production is increased by growth hormone and glucocorticoids. Functions of thyroid peroxidase include oxidation, organification of iodine, and coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT). Inhibited by PTU and methimazole. DIT + DIT = $T_4$. DIT + MIT = $T_3$. Wolff-Chaikoff effect—protective autoregulation; sudden exposure to excess iodine temporarily turns off thyroid peroxidase → ↓ $T_3$/$T_4$ production.

**FUNCTION**

Only free hormone is active. $T_3$ binds nuclear receptor with greater affinity than $T_4$. $T_3$ functions —7 B's:

- Brain maturation
- Bone growth (synergism with GH)
- β-adrenergic effects. ↑ $\beta_1$ receptors in heart → ↑ CO, HR, SV, contractility; β-blockers alleviate adrenergic symptoms in thyrotoxicosis
- Basal metabolic rate ↑ (via ↑ $Na^+/K^+$-ATPase → ↑ $O_2$ consumption, RR, body temperature)
- Blood sugar (↑ glycogenolysis, gluconeogenesis)
- Break down lipids (↑ lipolysis)
- Stimulates surfactant synthesis in Babies

**REGULATION**

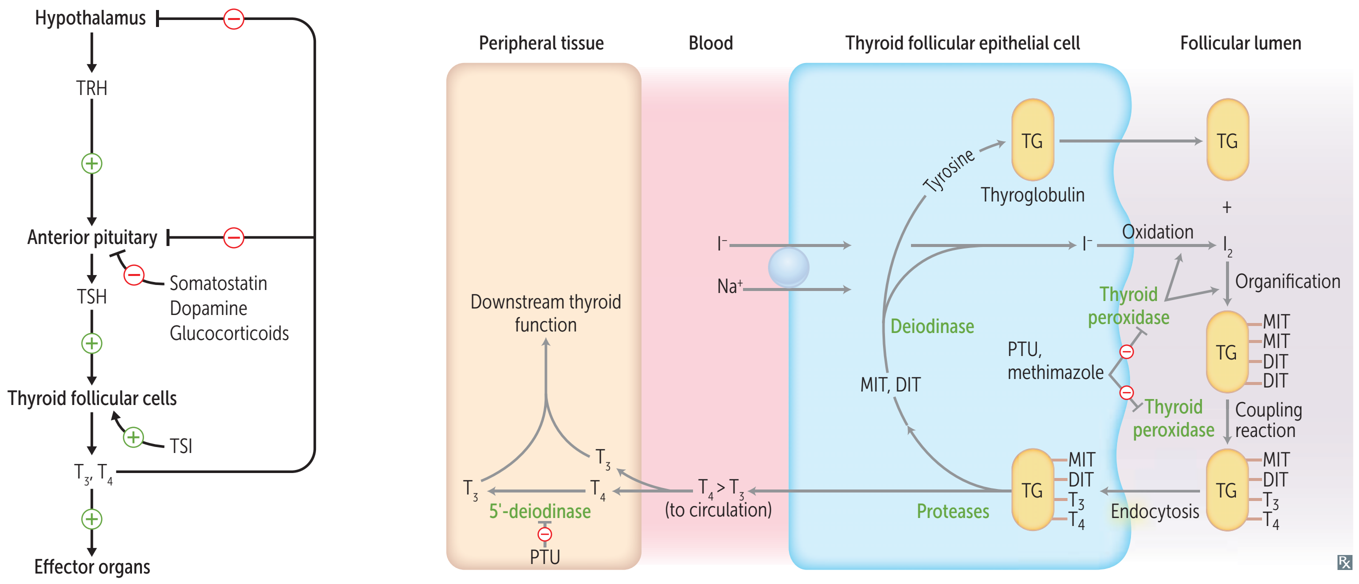
TRH → ⊕ TSH release → ⊕ follicular cells. Thyroid-stimulating immunoglobulin (TSI) may ⊕ follicular cells in Graves disease.

Negative feedback primarily by free $T_3$/$T_4$:

- Anterior pituitary → ↓ sensitivity to TRH
- Hypothalamus → ↓ TRH secretion

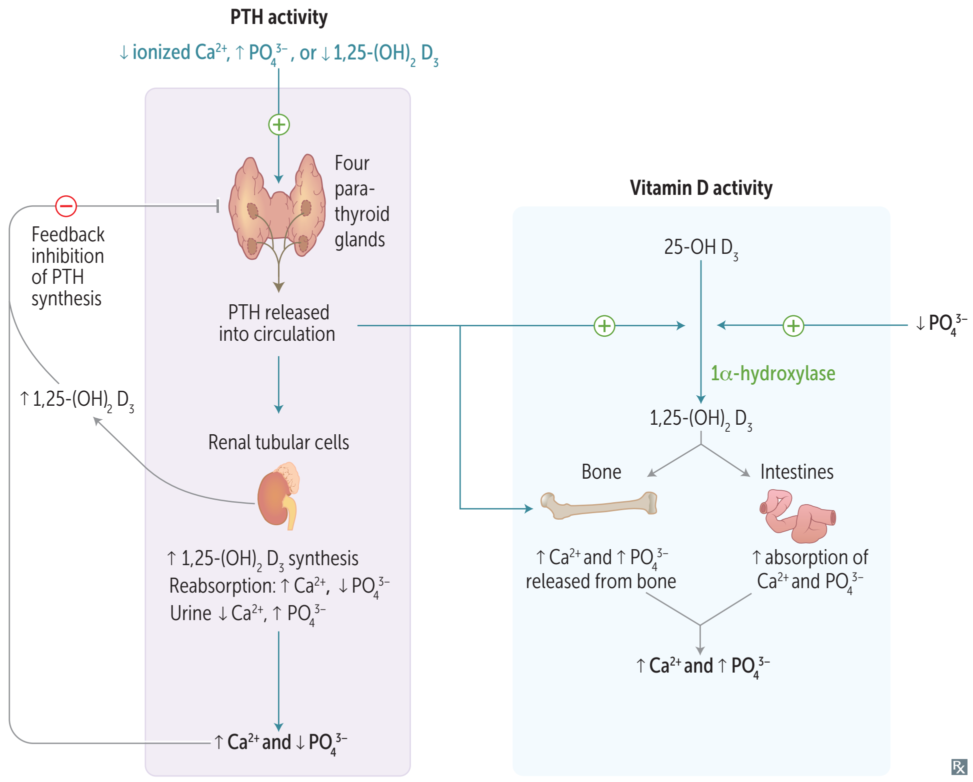
Thyroxine-binding globulin (TBG) binds most $T_3$/$T_4$ in blood. Bound $T_3$/$T_4$ = inactive.

- ↑ TBG in pregnancy, OCP use (estrogen → ↑ TBG) → ↑ total $T_3$/$T_4$
- ↓ TBG in steroid use, nephrotic syndrome



## Parathyroid hormone

| | | |
|---|---|---|
| SOURCE | Chief cells of parathyroid | |
| FUNCTION | ↑ free $Ca^{2+}$ in the blood (1° function)<br>↑ $Ca^{2+}$ and $PO_4^{3-}$ absorption in GI system<br>↑ $Ca^{2+}$ and $PO_4^{3-}$ from bone resorption<br>↑ $Ca^{2+}$ reabsorption from DCT<br>↓ $PO_4^{3-}$ reabsorption in PCT<br>↑ 1,25-$(OH)_2D_3$ (calci**tri**ol) production by activating 1α-hydroxylase in **PCT** (**tri** to make $D_3$ in the **PCT**) | PTH ↑ serum $Ca^{2+}$, ↓ serum $PO_4^{3-}$, ↑ urine $PO_4^{3-}$, ↑ urine cAMP<br>↑ RANK-L (receptor activator of NF-κB ligand) secreted by osteoblasts and osteocytes; binds RANK (receptor) on osteoclasts and their precursors to stimulate osteoclasts and ↑ $Ca^{2+}$ → bone resorption (intermittent PTH release can also stimulate bone formation)<br>**PTH** = **P**hosphate-**T**rashing **H**ormone<br>PTH-related peptide (PTHrP) functions like PTH and is commonly increased in malignancies (eg, squamous cell carcinoma of the lung, renal cell carcinoma) |
| REGULATION | ↓ serum $Ca^{2+}$ → ↑ PTH secretion<br>↑ serum $PO_4^{3-}$ → ↑ PTH secretion<br>↓ serum $Mg^{2+}$ → ↑ PTH secretion<br>↓↓ serum $Mg^{2+}$ → ↓ PTH secretion<br>Common causes of ↓ $Mg^{2+}$ include diarrhea, aminoglycosides, diuretics, alcohol use disorder | |



## Calcium homeostasis

Plasma $Ca^{2+}$ exists in three forms:
- Ionized/free (~ 45%, active form)
- Bound to albumin (~ 40%)
- Bound to anions (~ 15%)

↑ pH (less $H^+$) → albumin binds more $Ca^{2+}$ → ↓ ionized $Ca^{2+}$ (eg, cramps, pain, paresthesias, carpopedal spasm) → ↑ PTH

↓ pH (more $H^+$) → albumin binds less $Ca^{2+}$ → ↑ ionized $Ca^{2+}$ → ↓ PTH

Ionized/free $Ca^{2+}$ is 1° regulator of PTH; changes in pH alter PTH secretion, whereas changes in albumin concentration do not

## Calcitonin

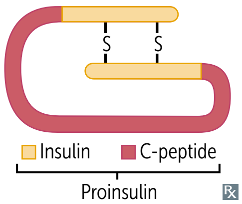
| | | |
|---|---|---|
| SOURCE | Parafollicular cells (C cells) of thyroid. | Calcitonin opposes actions of PTH. Not important in normal $Ca^{2+}$ homeostasis<br>Calcit**on**in t**on**es down serum $Ca^{2+}$ levels and keeps it in b**on**es |
| FUNCTION | ↓ bone resorption. | |
| REGULATION | ↑ serum $Ca^{2+}$ → ↑ calcitonin secretion. | |

## Glucagon

| | |
|---|---|
| SOURCE | Made by α cells of pancreas. |
| FUNCTION | Promotes glycogenolysis, gluconeogenesis, lipolysis, ketogenesis. Elevates blood sugar levels to maintain homeostasis when bloodstream glucose levels fall too low (ie, fasting state). |
| REGULATION | Secreted in response to hypoglycemia. Inhibited by insulin, amylin, somatostatin, hyperglycemia. |

## Insulin

**SYNTHESIS**




Preproinsulin (synthesized in RER of pancreatic β cells) → cleavage of "presignal" → proinsulin (stored in secretory granules) → cleavage of proinsulin → exocytosis of insulin and C-peptide equally. Insulin and C-peptide are ↑ in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C-peptide.

**FUNCTION**

Binds **in**sulin receptors (tyrosine kinase activity ❶), **in**ducing glucose uptake (carrier-mediated transport) **in**to insulin-dependent tissue ❷ and gene transcription.

Anabolic effects of insulin:
- ↑ glucose transport in skeletal muscle and adipose tissue
- ↑ glycogen synthesis and storage
- ↑ triglyceride synthesis
- ↑ $Na^+$ retention (kidneys)
- ↑ protein synthesis (muscles)
- ↑ cellular uptake of $K^+$ and amino acids
- ↓ glucagon release
- ↓ lipolysis in adipose tissue

Unlike glucose, insulin does not cross placenta.

Insulin-dependent glucose transporters:
- GLUT4: adipose tissue, striated muscle (exercise can also ↑ GLUT4 expression)

Insulin-independent transporters:
- GLUT1: RBCs, brain, cornea, placenta
- GLUT**2** (**bi**directional): β islet cells, liver, kidney, GI tract (think **2**-way street)
- GLUT3: brain, placenta
- GLUT5 (fructose): spermatocytes, GI tract
- SGLT1/SGLT2 ($Na^+$-glucose cotransporters): kidney, small intestine

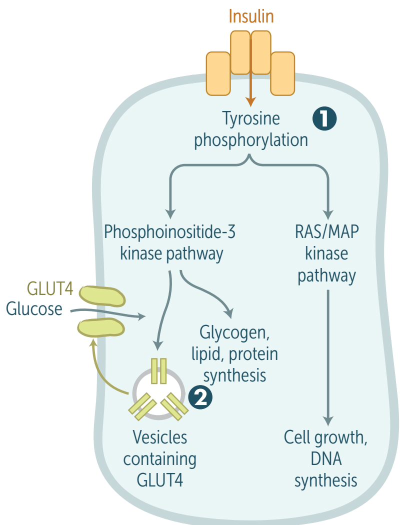
Brain prefers glucose, but may use ketone bodies during starvation. RBCs utilize glucose, as they lack mitochondria for aerobic metabolism.

**BRICK LIPS** (insulin-independent glucose uptake): **B**rain, **R**BCs, **I**ntestine, **C**ornea, **K**idney, **L**iver, **I**slet (β) cells, **P**lacenta, **S**permatocytes.

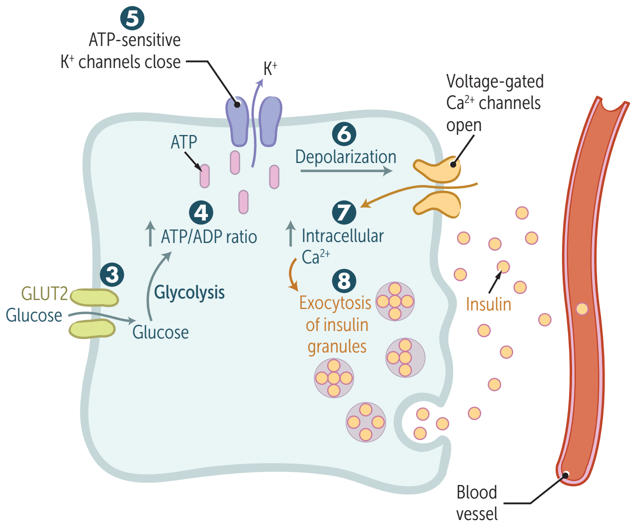
**REGULATION**

Glucose is the major regulator of insulin release. ↑ insulin response with oral vs IV glucose due to incretins (eg, glucagon-like peptide 1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP]), which are released after meals and ↑ β cell sensitivity to glucose. Release ↓ by $\alpha_2$, ↑ by $\beta_2$ stimulation (**2** = regulates **insulin**).

Glucose enters β cells ❸ → ↑ ATP generated from glucose metabolism ❹ closes $K^+$ channels (target of sulfonylureas) ❺ and depolarizes β cell membrane ❻. Voltage-gated $Ca^{2+}$ channels open → $Ca^{2+}$ influx ❼ and stimulation of insulin exocytosis ❽.

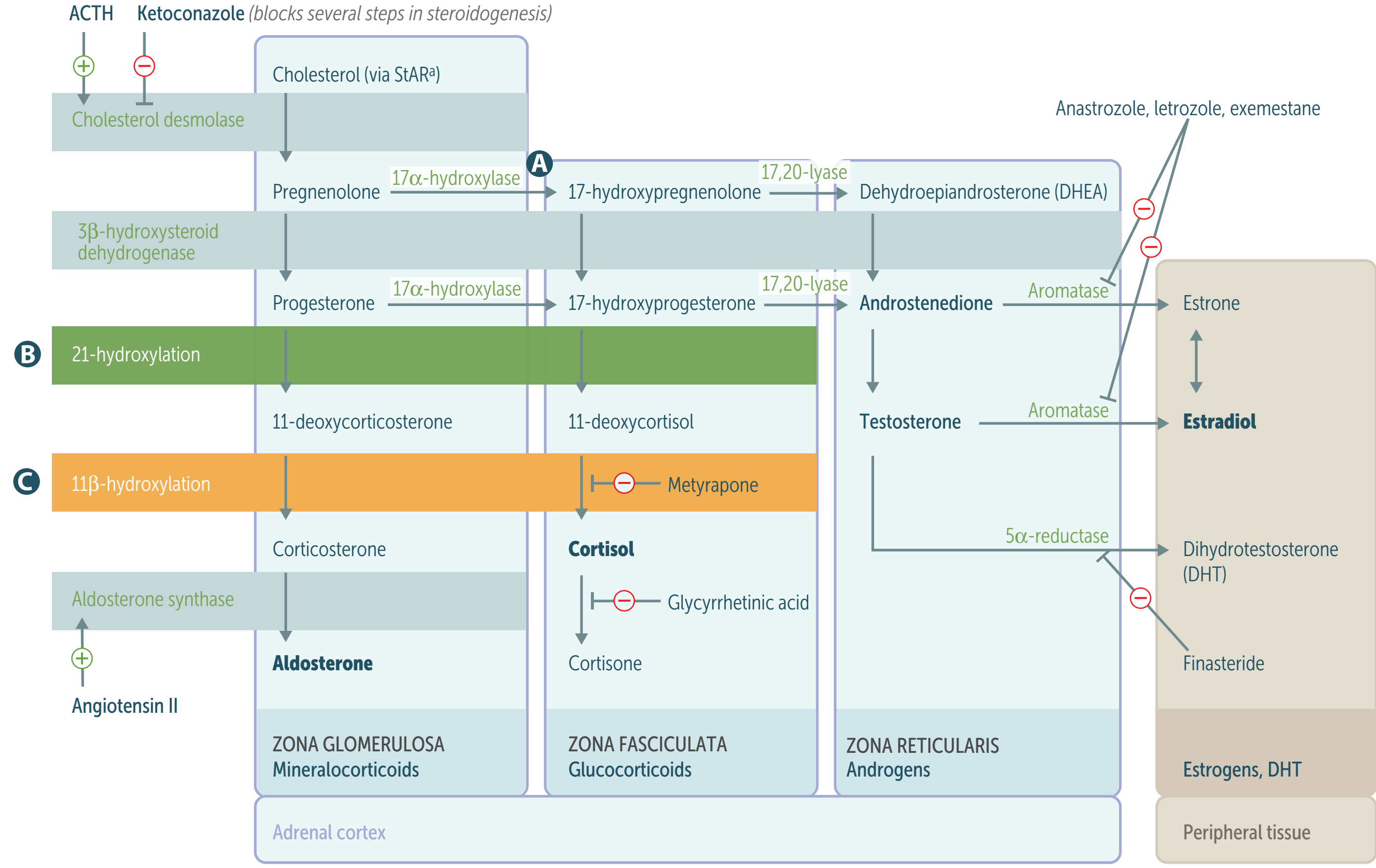



Insulin-dependent glucose uptake




Insulin secretion by pancreatic β cells

### Adrenal steroids and congenital adrenal hyperplasias



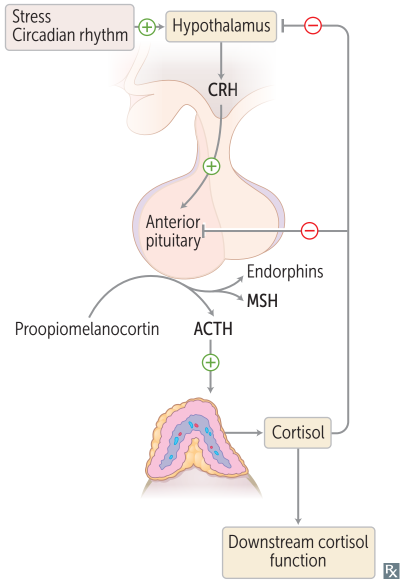

[a]Rate-limiting step.

| ENZYME DEFICIENCY | MINERALOCORTICOIDS | [K+] | BP | CORTISOL | SEX HORMONES | LABS | PRESENTATION |
|---|---|---|---|---|---|---|---|
| **A 17α-hydroxylase[a]** | ↑ | ↓ | ↑ | ↓ | ↓ | ↓ androstenedione | XY: ambiguous genitalia, undescended testes<br>XX: lacks 2° sexual development |
| **B 21-hydroxylase[a]** | ↓ | ↑ | ↓ | ↓ | ↑ | ↑ renin activity<br>↑ 17-hydroxy-progesterone | Most common<br>Presents in infancy (salt wasting) or childhood (precocious puberty)<br>XX: virilization |
| **C 11β-hydroxylase[a]** | ↓ aldosterone<br>↑ 11-deoxycorticosterone (results in ↑ BP) | ↓ | ↑ | ↓ | ↑ | ↓ renin activity | Presents in infancy (severe hypertension) or childhood (precocious puberty)<br>XX: virilization |

[a]All congenital adrenal enzyme deficiencies are autosomal recessive disorders and most are characterized by skin hyperpigmentation (due to ↑ MSH production, which is coproduced and secreted with ACTH) and bilateral adrenal gland enlargement (due to ↑ ACTH stimulation).

If deficient enzyme starts with 1, it causes hypertension; if deficient enzyme ends with 1, it causes virilization in females.

## Cortisol

| | | |
|---|---|---|
| SOURCE | Adrenal zona fasciculata. | Bound to corticosteroid-binding globulin. |
| FUNCTION | ↑ **A**ppetite<br>↑ **B**lood pressure:<br>▪ Upregulates $\alpha_1$-receptors on arterioles → ↑ sensitivity to norepinephrine and epinephrine (permissive action)<br>▪ At high concentrations, can bind to mineralocorticoid (aldosterone) receptors<br>↑ **I**nsulin resistance (diabetogenic)<br>↑ **G**luconeogenesis, lipolysis, and proteolysis (↓ glucose utilization)<br>↓ **F**ibroblast activity (poor wound healing, ↓ collagen synthesis, ↑ striae)<br>↓ **I**nflammatory and **I**mmune responses:<br>▪ Inhibits production of leukotrienes and prostaglandins<br>▪ Inhibits WBC adhesion → neutrophilia<br>▪ Blocks histamine release from mast cells<br>▪ Eosinopenia, lymphopenia<br>▪ Blocks IL-2 production<br>↓ **B**one formation (↓ osteoblast activity) | Cortisol is **A BIG FIB**.<br>Exogenous corticosteroids can cause reactivation of TB and candidiasis (blocks IL-2 production).<br><br> |
| REGULATION | CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata. Excess cortisol ↓ CRH, ACTH, and cortisol secretion. | Chronic stress may induce prolonged cortisol secretion, cortisol resistance, impaired immunocompetency, and dysregulation of HPA axis. |

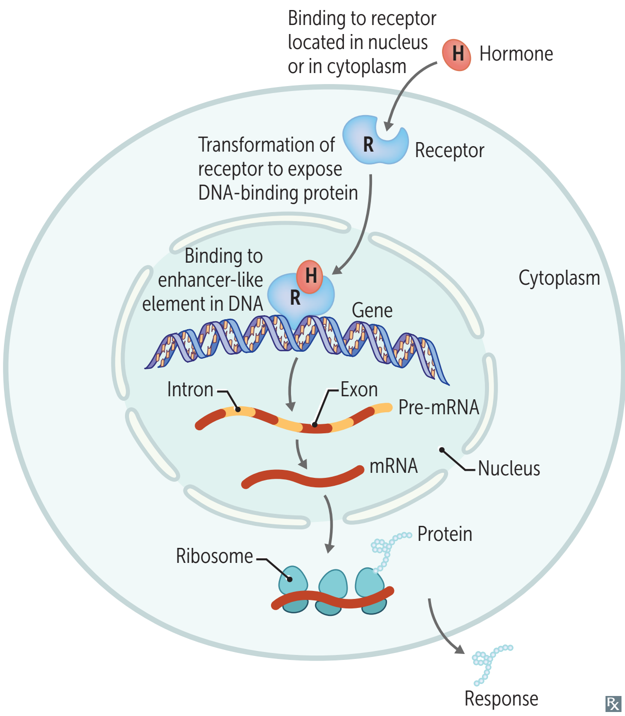
## Appetite regulation

| | |
|---|---|
| **Ghrelin** | Stimulates hunger (orexigenic effect) and GH release (via GH secretagog receptor). Produced by stomach. Sleep deprivation, fasting, or Prader-Willi syndrome → ↑ ghrelin production.<br>**Ghr**elin makes you **ghr**ow hun**ghr**y. Acts on lateral area of hypothalamus (hunger center) to ↑ appetite. |
| **Leptin** | Satiety hormone. Produced by adipose tissue. Mutation of leptin gene → severe obesity. Obese people have ↑ leptin due to ↑ adipose tissue but are tolerant or resistant to leptin's anorexigenic effect. Sleep deprivation or starvation → ↓ leptin production.<br>Lept**in** keeps you th**in**. Acts on ventromedial area of hypothalamus (satiety center) to ↓ appetite. |
| **Endocannabinoids** | Act at cannabinoid receptors in hypothalamus and nucleus accumbens, two key brain areas for the homeostatic and hedonic control of food intake → ↑ appetite.<br>Exogenous cannabinoids cause "the munchies." |

## Signaling pathways of endocrine hormones

| | | |
|---|---|---|
| **cAMP** | FSH, LH, ACTH, TSH, CRH, hCG, ADH ($V_2$-receptor), MSH, PTH, Calcitonin, Histamine ($H_2$-receptor), Glucagon, GHRH | FLAT ChAMPs CHuGG |
| **cGMP** | BNP, ANP, EDRF (NO) | BAD GraMPa<br>Think vasodilation and diuresis |
| **$IP_3$** | GnRH, Oxytocin, ADH ($V_1$-receptor), TRH, Histamine ($H_1$-receptor), Angiotensin II, Gastrin | GOAT HAG |
| **Intracellular receptor** | Progesterone, Estrogen, Testosterone, Cortisol, Aldosterone, $T_3$/$T_4$, Vitamin D | PET CAT in TV |
| **Receptor tyrosine kinase** | IGF-1, FGF, PDGF, EGF, Insulin | MAP kinase pathway<br>Get Found In the MAP |
| **Serine/threonine kinase receptor** | TGF-β | |
| **Nonreceptor tyrosine kinase** | G-CSF, Erythropoietin, Thrombopoietin<br>Prolactin, Immunomodulators (eg, cytokines IL-2, IL-6, IFN), GH | JAK/STAT pathway<br>Think acidophils and cytokines<br>GET a JAKed PIG |

## Signaling pathways of steroid hormones




Steroid hormones are lipophilic and therefore must circulate bound to specific binding globulins, which ↑ their solubility.

In males, ↑ sex hormone–binding globulin (SHBG) lowers free testosterone → gynecomastia.

In females, ↓ SHBG raises free testosterone → hirsutism.

↑ estrogen (eg, OCPs, pregnancy) → ↑ SHBG.

## ▸ ENDOCRINE—PATHOLOGY

### Syndrome of inappropriate antidiuretic hormone secretion

Characterized by:
- Excessive free water retention
- Euvolemic hyponatremia with continued urinary $Na^+$ excretion
- Urine osmolality > serum osmolality

Body responds to water retention with ↓ aldosterone and ↑ ANP and BNP → ↑ urinary $Na^+$ secretion → normalization of extracellular fluid volume → euvolemic hyponatremia. Very low serum $Na^+$ levels can lead to cerebral edema, seizures. Correct slowly to prevent osmotic demyelination syndrome (formerly called central pontine myelinolysis).

SIADH causes include (**HELD**-up water):
- **H**ead trauma/CNS disorders
- **E**ctopic ADH (eg, small cell lung cancer)
- **L**ung disease
- **D**rugs (eg, SSRIs, carbamazepine, cyclophosphamide)

Treatment: fluid restriction (first line), salt tablets, IV hypertonic saline, diuretics, ADH antagonists (eg, conivaptan, tolvaptan, demeclocycline).

### Primary polydipsia and diabetes insipidus

Characterized by the production of large amounts of dilute urine +/– thirst. Urine specific gravity <1.006. Urine osmolality usually <300 mOsm/kg. Diabetes insipidus (DI) is classified as central or nephrogenic depending on etiology.

| | Primary polydipsia | Central DI | Nephrogenic DI |
|---|---|---|---|
| DEFINITION | Excessive water intake | ↓ ADH release | ADH resistance |
| CAUSES | Psychiatric illnesses, hypothalamic lesions affecting thirst center | Idiopathic, tumors (eg, pituitary), infiltrative diseases (eg, sarcoidosis), trauma, surgery, hypoxic encephalopathy | Hereditary (ADH receptor mutation), drugs (eg, lithium, demeclocycline), hypercalcemia, hypokalemia |
| SERUM OSMOLALITY | ↓ | ↑ | ↑ |
| ADH LEVEL | ↓ or normal | ↓ | Normal or ↑ |
| WATER RESTRICTION[a] | Significant ↑ in urine osmolality (>700 mOsm/kg) | No change or slight ↑ in urine osmolality | No change or slight ↑ in urine osmolality |
| DESMOPRESSIN ADMINISTRATION[b] | — | Significant ↑ in urine osmolality (>50%) | Minimal change in urine osmolality |
| TREATMENT | Water restriction | Desmopressin | Manage the underlying cause. Low-solute diet, HCTZ, amiloride, indomethacin |

[a]No water intake for 2-3 hours followed by hourly measurements of urine volume and osmolality as well as plasma $Na^+$ concentration and osmolality.

[b]Desmopressin (ADH analog) is administered if serum osmolality >295-300 mOsm/kg, plasma $Na^+ \geq 145$ mEq/L, or urine osmolality does not rise despite ↑ plasma osmolality.

**Hypopituitarism**

Undersecretion of pituitary hormones due to:

- Nonsecreting pituitary adenoma, craniopharyngioma
- Sheehan syndrome—ischemic infarct of pituitary following postpartum bleeding; pregnancy-induced pituitary growth → ↑ susceptibility to hypoperfusion. Usually presents with failure to lactate, absent menstruation, cold intolerance
- Empty sella syndrome—atrophy or compression of pituitary (which lies in the sella turcica), often idiopathic, common in obese females; associated with idiopathic intracranial hypertension
- Pituitary apoplexy—sudden hemorrhage of pituitary gland, often in the presence of an existing pituitary adenoma. Usually presents with sudden onset severe headache, visual impairment (eg, bitemporal hemianopia, diplopia due to CN III palsy), and features of hypopituitarism
- Brain injury
- Radiation

Treatment: hormone replacement therapy (corticosteroids, thyroxine, sex steroids, human growth hormone)

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**Acromegaly**

Excess GH in adults. Typically caused by pituitary adenoma.

FINDINGS

Large tongue with deep furrows, deep voice, large hands and feet, coarsening of facial features with aging A, frontal bossing, diaphoresis (excessive sweating), impaired glucose tolerance (insulin resistance), hypertension. ↑ risk of colorectal polyps and cancer.

↑ GH in children → gigantism (↑ linear bone growth). HF most common cause of death.


DIAGNOSIS

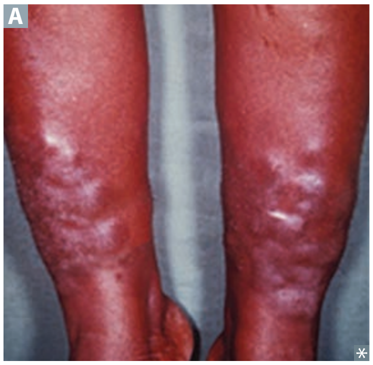
↑ serum IGF-1; failure to suppress serum GH following oral glucose tolerance test; pituitary mass seen on brain MRI.

TREATMENT

Pituitary adenoma resection. If not cured, treat with octreotide (somatostatin analog), pegvisomant (GH receptor antagonist), or dopamine agonists (eg, cabergoline).

## Hypothyroidism vs hyperthyroidism

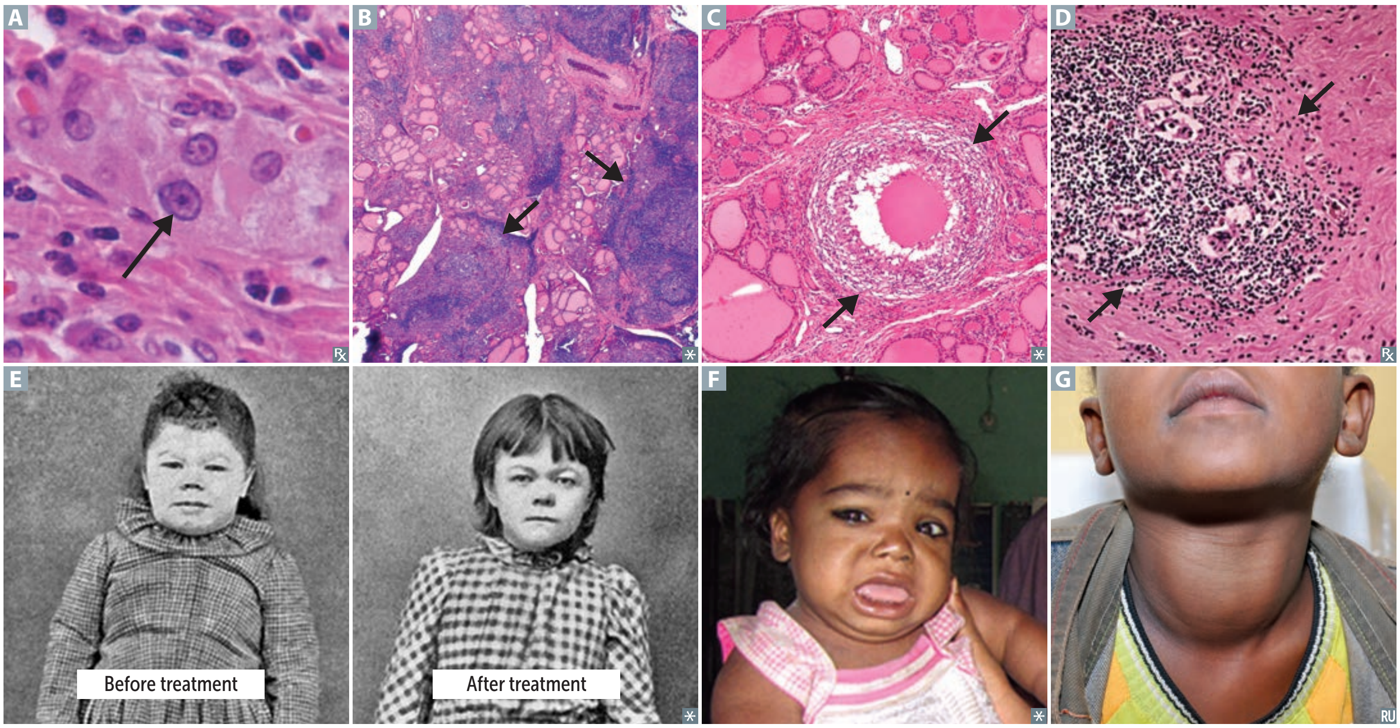
| | Hypothyroidism | Hyperthyroidism |
|---|---|---|
| METABOLIC | Cold intolerance, ↓ sweating, weight gain (↓ basal metabolic rate → ↓ calorigenesis), hyponatremia (↓ free water clearance) | Heat intolerance, ↑ sweating, weight loss (↑ synthesis of $Na^+$-$K^+$ ATPase → ↑ basal metabolic rate → ↑ calorigenesis) |
| SKIN/HAIR | Dry, cool skin (due to ↓ blood flow); coarse, brittle hair; diffuse alopecia; brittle nails; puffy facies and generalized nonpitting edema (myxedema A) due to ↑ GAGs in interstitial spaces → ↑ osmotic pressure → water retention | Warm, moist skin (due to vasodilation); fine hair; onycholysis (B); pretibial myxedema in Graves disease |
| OCULAR | Periorbital edema C | Ophthalmopathy in Graves disease (including periorbital edema, exophthalmos), lid lag/retraction (↑ sympathetic stimulation of levator palpebrae superioris and superior tarsal muscle) |
| GASTROINTESTINAL | Constipation (↓ GI motility), ↓ appetite | Hyperdefecation/diarrhea (↑ GI motility), ↑ appetite |
| MUSCULOSKELETAL | Hypothyroid myopathy (proximal weakness, ↑ CK), carpal tunnel syndrome, myoedema (small lump rising on the surface of a muscle when struck with a hammer) | Thyrotoxic myopathy (proximal weakness, normal CK), osteoporosis/↑ fracture rate ($T_3$ directly stimulates bone resorption) |
| REPRODUCTIVE | Abnormal uterine bleeding, ↓ libido, infertility | Abnormal uterine bleeding, gynecomastia, ↓ libido, infertility |
| NEUROPSYCHIATRIC | Hypoactivity, lethargy, fatigue, weakness, depressed mood, ↓ reflexes (delayed/slow relaxing) | Hyperactivity, restlessness, anxiety, insomnia, fine tremors (due to ↑ β-adrenergic activity), ↑ reflexes (brisk) |
| CARDIOVASCULAR | Bradycardia, dyspnea on exertion (↓ cardiac output) | Tachycardia, palpitations, dyspnea, arrhythmias (eg, atrial fibrillation), chest pain and systolic HTN due to ↑ number and sensitivity of β-adrenergic receptors, ↑ expression of cardiac sarcolemmal ATPase and ↓ expression of phospholamban |
| LABS | ↑ TSH (if 1°)<br>↓ free $T_3$ and $T_4$<br>Hypercholesterolemia (due to ↓ LDL receptor expression) | ↓ TSH (if 1°)<br>↑ free $T_3$ and $T_4$<br>↓ LDL, HDL, and total cholesterol |



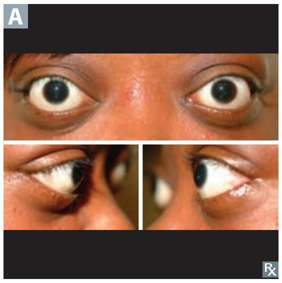


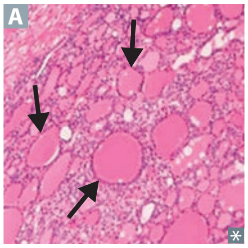
## Hypothyroidism

| | |
|---|---|
| **Hashimoto thyroiditis** | Also called chronic autoimmune thyroiditis. Most common cause of hypothyroidism in iodine-sufficient regions. Associated with HLA-DR3, ↑ risk of primary thyroid lymphoma (typically diffuse large B-cell lymphoma).<br>Findings: moderately enlarged, **nontender** thyroid. May be preceded by transient hyperthyroid state ("Hashitoxicosis") due to follicular rupture and thyroid hormone release.<br>Serology: ⊕ antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies.<br>Histology: Hürthle cells A, lymphoid aggregates with germinal centers B.<br>Postpartum thyroiditis—mild, self-limited variant of Hashimoto thyroiditis arising < 1 year after delivery. |
| **Subacute granulomatous thyroiditis** | Also called de Quervain thyroiditis. Usually, a self-limited disease. Natural history: transient hyperthyroidism → euthyroid state → hypothyroidism. Often preceded by viral infection.<br>Findings: ↑ ESR, jaw pain, very **tender** thyroid (de Quervain is associated with pain).<br>Histology: granulomatous inflammation C. |
| **Riedel thyroiditis** | Also called invasive fibrous thyroiditis. May be part of IgG$_4$-related disease (eg, autoimmune pancreatitis, retroperitoneal fibrosis, noninfectious aortitis). Hypothyroidism occurs in ⅓ of patients. Fibrosis may extend to local structures (eg, trachea, esophagus), mimicking anaplastic carcinoma.<br>Findings: slowly enlarging, hard (rock-like), fixed, **nontender** thyroid.<br>Histology: thyroid replaced by fibrous tissue and inflammatory infiltrate D. |
| **Congenital hypothyroidism** | Formerly called cretinism. Most commonly caused by thyroid dysgenesis (abnormal thyroid gland development; eg, agenesis, hypoplasia, ectopy) or dyshormonogenesis (abnormal thyroid hormone synthesis; eg, mutations in thyroid peroxidase) in iodine-sufficient regions.<br>Findings (6 P's): pot-bellied, pale, puffy-faced child E with protruding umbilicus, protuberant tongue F, and poor brain development. |
| **Other causes** | Iodine deficiency (most common cause worldwide; typically presents with goiter G), iodine excess (Wolff-Chaikoff effect), drugs (eg, amiodarone, lithium), nonthyroidal illness syndrome (also called euthyroid sick syndrome; ↓ $T_3$ with normal/↓ $T_4$ and TSH in critically ill patients). |



## Hyperthyroidism

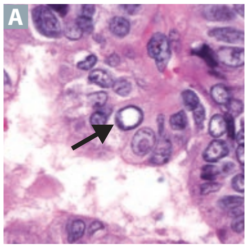
| | |
|---|---|
| **Graves disease**  | Most common cause of hyperthyroidism. Thyroid-stimulating immunoglobulin (IgG, can cause transient neonatal hyperthyroidism; type II hypersensitivity) stimulates TSH receptors on thyroid (hyperthyroidism, diffuse goiter), dermal fibroblasts (pretibial myxedema), and orbital fibroblasts (Graves orbitopathy). Activation of T-cells → lymphocytic infiltration of retroorbital space → ↑ cytokines (eg, TNF-$\alpha$, IFN-$\gamma$) → ↑ fibroblast secretion of hydrophilic GAGs → ↑ osmotic muscle swelling, muscle inflammation, and adipocyte count → exophthalmos A. Often presents during stress (eg, pregnancy). Associated with HLA-DR3 and HLA-B8.<br>Histology: tall, crowded follicular epithelial cells; scalloped colloid. |
| **Toxic multinodular goiter** | Focal patches of hyperfunctioning follicular cells distended with colloid working independently of TSH (due to TSH receptor mutations in 60% of cases). ↑ release of $T_3$ and $T_4$. Hot nodules are rarely malignant. |
| **Thyroid storm** | Uncommon but serious complication that occurs when hyperthyroidism is incompletely treated/untreated and then significantly worsens in the setting of acute stress such as infection, trauma, surgery. Presents with agitation, delirium, fever, diarrhea, coma, and tachyarrhythmia (cause of death). May see ↑ LFTs. Treat with the 4 P's: β-blockers (eg, propranolol), propylthiouracil, corticosteroids (eg, prednisolone), potassium iodide (Lugol iodine). Iodide load → ↓ $T_4$ synthesis → Wolff-Chaikoff effect. |
| **Jod-Basedow phenomenon** | Iodine-induced hyperthyroidism. Occurs when a patient with iodine deficiency and partially autonomous thyroid tissue (eg, autonomous nodule) is made iodine replete. Can happen after iodine IV contrast or amiodarone use. Opposite to Wolff-Chaikoff effect. |
| **Causes of goiter** | Smooth/diffuse: Graves disease, Hashimoto thyroiditis, iodine deficiency, TSH-secreting pituitary adenoma.<br>Nodular: toxic multinodular goiter, thyroid adenoma, thyroid cancer, thyroid cyst. |

| | |
|---|---|
| **Thyroid adenoma**  | Benign solitary growth of the thyroid. Most are nonfunctional ("cold"), can rarely cause hyperthyroidism via autonomous thyroid hormone production ("hot" or "toxic"). Most common histology is follicular (arrows in A); absence of capsular or vascular invasion (unlike follicular carcinoma). |

**Thyroid cancer**

Typically diagnosed with fine needle aspiration; treated with thyroidectomy. Complications of surgery include hypocalcemia (due to removal of parathyroid glands), transection of recurrent laryngeal nerve during ligation of inferior thyroid artery (leads to dysphagia and dysphonia [hoarseness]), and injury to the external branch of the superior laryngeal nerve during ligation of superior thyroid vascular pedicle (may lead to loss of tenor usually noticeable in professional voice users).

**Papillary carcinoma**



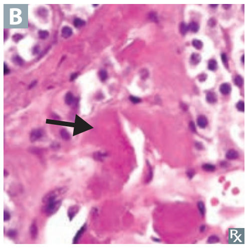

Most common. Empty-appearing nuclei with central clearing ("**Orphan Annie**" eyes) A, psam**Moma** bodies, nuclear grooves (**Papi** and **Moma** adopted **Orphan Annie**). ↑ risk with *RET/PTC* rearrangements and *BRAF* mutations, childhood irradiation.

**P**apillary carcinoma: most **p**revalent, **p**alpable lymph nodes. Good prognosis.

**Follicular carcinoma**

Good prognosis. Invades thyroid capsule and vasculature (unlike follicular adenoma), uniform follicles; hematogenous spread is common. Associated with *RAS* mutation and *PAX8-PPAR-γ* translocations. Fine needle aspiration cytology may not be able to distinguish between follicular adenoma and carcinoma.

**Medullary carcinoma**

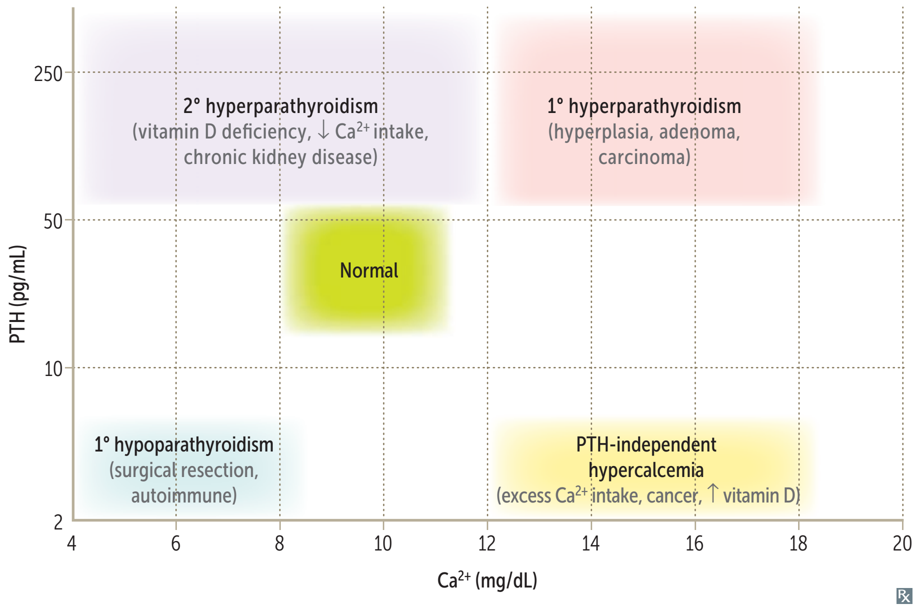



From parafollicular "**C** cells"; produces **c**alcitonin, sheets of polygonal cells in an amyloid stroma B (stains with **C**ongo red). Associated with MEN 2A and 2B (*RET* mutations).

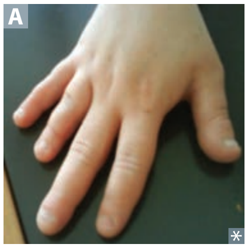
**Undifferentiated/anaplastic carcinoma**

Older patients; presents with rapidly enlarging neck mass → compressive symptoms (eg, dyspnea, dysphagia, hoarseness); very poor prognosis. Associated with *TP53* mutation.

## Diagnosing parathyroid disease




## Hypoparathyroidism



Due to injury to parathyroid glands or their blood supply (usually during surgery), autoimmune destruction, or DiGeorge syndrome. Findings: tetany, hypocalcemia, hyperphosphatemia.

Chvostek sign—tapping of facial nerve (tap the Cheek) → contraction of facial muscles.

Trousseau sign—occlusion of brachial artery with BP cuff (cuff the Triceps) → carpal spasm.

**Pseudohypoparathyroidism type 1A**—autosomal dominant, maternally transmitted mutations (imprinted GNAS gene). GNAS1-inactivating mutation (coupled to PTH receptor) that encodes the $G_s$ protein α subunit → inactivation of adenylate cyclase when PTH binds to its receptor → end-organ resistance (kidney and bone) to PTH.

Physical findings: Albright hereditary osteodystrophy (shortened 4th/5th digits A, short stature, round face, subcutaneous calcifications, developmental delay).

Labs: ↑ PTH, ↓ $Ca^{2+}$, ↑ $PO_4^{3-}$.

**Pseudopseudohypoparathyroidism**—autosomal dominant, paternally transmitted mutations (imprinted GNAS gene) but without end-organ resistance to PTH due to normal maternal allele maintaining renal responsiveness to PTH.

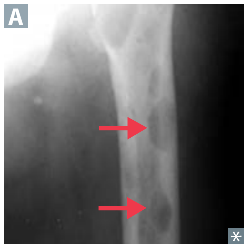
Physical findings: same as Albright hereditary osteodystrophy.

Labs: normal PTH, $Ca^{2+}$, $PO_4^{3-}$.

## Lab values in hypocalcemia

| DISORDER | $Ca^{2+}$ | $PO_4^{3-}$ | PTH |
|---|---|---|---|
| Vitamin D deficiency | ↓ | ↓ | ↑ |
| Hypoparathyroidism | ↓ | ↑ | ↓ |
| 2° hyperparathyroidism (CKD) | ↓ | ↑ | ↑ |
| Pseudohypoparathyroidism | ↓ | ↑ | ↑ |
| Hyperphosphatemia | ↓ | ↑ | ↑ |

## Hyperparathyroidism

| | | |
|---|---|---|
| **Primary hyperparathyroidism**  | Usually due to parathyroid adenoma or hyperplasia. **Hypercalcemia**, hypercalciuria (renal **stones**), polyuria (**thrones**), hypophosphatemia, ↑ PTH, ↑ ALP, ↑ urinary cAMP. Most often asymptomatic. May present with **bone** pain, weakness, constipation ("**groans**"), abdominal/flank pain (kidney stones, acute pancreatitis), neuropsychiatric disturbances ("**psychiatric overtones**"). | **Osteitis fibrosa cystica**—cystic **bone** spaces filled with brown fibrous tissue A ("brown tumor" consisting of osteoclasts and deposited hemosiderin from hemorrhages; causes bone pain). Due to ↑ PTH, classically associated with 1° (but also seen with 2°) hyperparathyroidism. "**Stones**, **thrones**, **bones**, **groans**, and **psychiatric overtones**." |
| **Secondary hyperparathyroidism** | 2° hyperplasia due to ↓ $Ca^{2+}$ absorption and/or ↑ $PO_4^{3-}$, most often in chronic kidney disease (causes hypovitaminosis D and hyperphosphatemia → ↓ $Ca^{2+}$). **Hypocalcemia**, hyperphosphatemia in chronic kidney disease (vs hypophosphatemia with most other causes), ↑ ALP, ↑ PTH. | **Renal osteodystrophy**—renal disease → 2° and 3° hyperparathyroidism → bone lesions. |
| **Tertiary hyperparathyroidism** | Refractory (autonomous) hyperparathyroidism resulting from chronic kidney disease. ↑↑ PTH, ↑ $Ca^{2+}$. | |

| | |
|---|---|
| **Familial hypocalciuric hypercalcemia** | Defective G-coupled $Ca^{2+}$-sensing receptors in multiple tissues (eg, parathyroids, kidneys). Higher than normal $Ca^{2+}$ levels required to suppress PTH. Excessive renal $Ca^{2+}$ reabsorption → mild hypercalcemia and hypocalciuria with normal to ↑ PTH levels. |

## Diabetes mellitus

**ACUTE MANIFESTATIONS**

Polydipsia, polyuria, polyphagia, weight loss, DKA (type 1), hyperosmolar hyperglycemic state (type 2).

Rarely, can be caused by unopposed secretion of GH and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).

**CHRONIC COMPLICATIONS**

Nonenzymatic glycation:

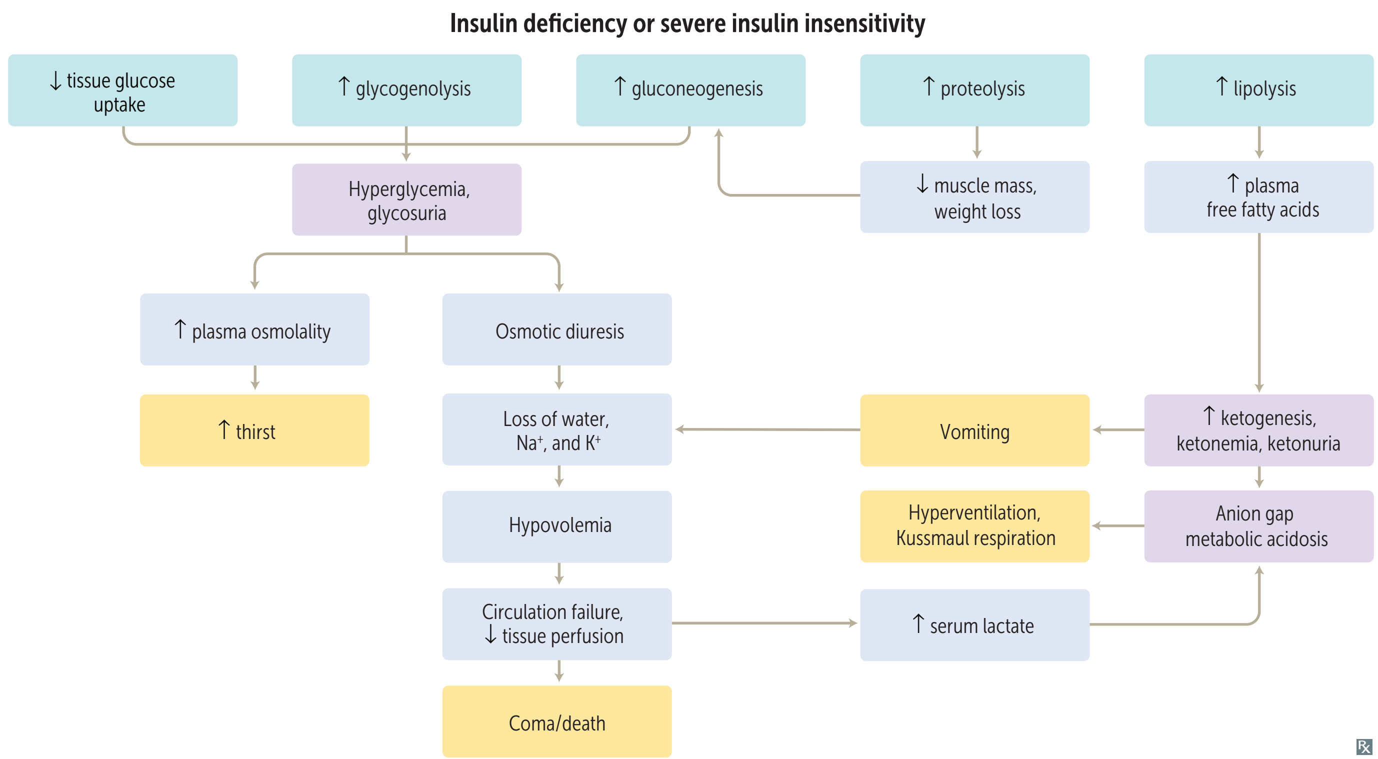
- Small vessel disease (diffuse thickening of basement membrane) → retinopathy (hemorrhage, exudates, microaneurysms, vessel proliferation), glaucoma, nephropathy. Nodular glomerulosclerosis → progressive proteinuria (initially microalbuminuria; ACE inhibitors and ARBs are renoprotective. Arteriolosclerosis (causing hypertension) → chronic kidney disease.
- Large vessel atherosclerosis, CAD, peripheral vascular occlusive disease, gangrene → limb loss, cerebrovascular disease. MI most common cause of death.

Osmotic damage (sorbitol accumulation in organs with aldose reductase and ↓ or absent sorbitol dehydrogenase):

- Neuropathy: motor, sensory (glove and stocking distribution), autonomic degeneration (eg, GERD, gastroparesis, diabetic diarrhea).
- Cataracts.

**DIAGNOSIS**

| TEST | DIAGNOSTIC CUTOFF | NOTES |
|---|---|---|
| $HbA_{1c}$ | ≥ 6.5% | Reflects average blood glucose over prior 3 months (influenced by RBC turnover) |
| Fasting plasma glucose | ≥ 126 mg/dL | Fasting for > 8 hours |
| 2-hour oral glucose tolerance test | ≥ 200 mg/dL | 2 hours after consumption of 75 g of glucose in water |
| Random plasma glucose | ≥ 200 mg/dL | Presence of hyperglycemic symptoms is required |



### Type 1 vs type 2 diabetes mellitus

| | Type 1 | Type 2 |
|---|---|---|
| 1° DEFECT | Autoimmune T-cell–mediated destruction of β cells (eg, due to presence of glutamic acid decarboxylase antibodies) | ↑ resistance to insulin, progressive pancreatic β-cell failure |
| INSULIN NECESSARY IN TREATMENT | Always | Sometimes |
| AGE (EXCEPTIONS COMMON) | < 30 yr | > 40 yr |
| ASSOCIATION WITH OBESITY | No | Yes |
| GENETIC PREDISPOSITION | Relatively weak (50% concordance in identical twins), polygenic | Relatively strong (90% concordance in identical twins), polygenic |
| ASSOCIATION WITH HLA SYSTEM | Yes, HLA-DR4 and -DR3 (4 – 3 = type 1) | No |
| GLUCOSE INTOLERANCE | Severe | Mild to moderate |
| INSULIN SENSITIVITY | High | Low |
| KETOACIDOSIS | Common | Rare |
| β-CELL NUMBERS IN THE ISLETS | ↓ | Variable (with amyloid deposits) |
| SERUM INSULIN LEVEL | ↓ | ↑ initially, but ↓ in advanced disease |
| CLASSIC SYMPTOMS OF POLYURIA, POLYDIPSIA, POLYPHAGIA, WEIGHT LOSS | Common | Sometimes |
| HISTOLOGY | Islet leukocytic infiltrate | Islet amyloid polypeptide (IAPP) deposits |

### Hyperglycemic emergencies

| | Diabetic ketoacidosis | Hyperosmolar hyperglycemic state |
|---|---|---|
| PATHOGENESIS | Insulin noncompliance or ↑ requirements due to ↑ stress (eg, infection) → excess lipolysis and ↑ ketogenesis from ↑ free fatty acids → ketone bodies (β-hydroxybutyrate > acetoacetate). **Insulin deficient, ketones present.** | Profound hyperglycemia → excessive osmotic diuresis → dehydration and ↑ serum osmolality → HHS. Classically seen in elderly patients with type 2 DM and limited ability to drink. **Insulin present, ketones absent.** |
| SIGNS/SYMPTOMS | **DKA** is **D**eadly: **D**elirium/psychosis, **K**ussmaul respirations (rapid, deep breathing), **A**bdominal pain/nausea/vomiting, **D**ehydration. Fruity breath odor due to exhaled acetone. | Thirst, polyuria, lethargy, focal neurologic deficits, seizures. |
| LABS | Hyperglycemia, ↑ $H^+$, ↓ $HCO_3^-$ (↑ anion gap metabolic acidosis), ↑ urine and blood ketone levels, leukocytosis. Normal/↑ serum $K^+$, but depleted intracellular $K^+$ due to transcellular shift from ↓ insulin and acidosis. Osmotic diuresis → ↑ $K^+$ loss in urine → total body $K^+$ depletion. | Hyperglycemia (often > 600 mg/dL), ↑ serum osmolality (> 320 mOsm/kg), normal pH (no acidosis), no ketones. Normal/↑ serum $K^+$, ↓ intracellular $K^+$. |
| COMPLICATIONS | Life-threatening mucormycosis, cerebral edema, cardiac arrhythmias. | Can progress to coma and death if untreated. |
| TREATMENT | IV fluids, IV insulin, and $K^+$ (to replete intracellular stores). Glucose may be required to prevent hypoglycemia from insulin therapy. | |

### Hypoglycemia in diabetes mellitus

Usually occurs in patients treated with insulin or insulin secretagogues (eg, sulfonylureas, meglitinides) in the setting of high-dose treatment, inadequate food intake, and/or exercise.

- Neurogenic/autonomic symptoms: diaphoresis, tachycardia, tremor, anxiety, hunger. May allow perception of ↓ glucose (hypoglycemia awareness).
- Neuroglycopenic symptoms: altered mental status, seizures, death due to insufficient glucose in CNS.

Treatment: simple carbohydrates (eg, glucose tablets, fruit juice), IM glucagon, IV dextrose.

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## Cushing syndrome

**ETIOLOGY**

↑ cortisol due to a variety of causes:

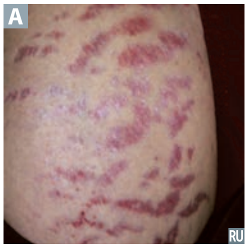
- Exogenous corticosteroids → ↓ ACTH → bilateral adrenal atrophy. Most common cause.
- Primary adrenal adenoma, hyperplasia, or carcinoma → ↓ ACTH → atrophy of uninvolved adrenal gland.
- ACTH-secreting pituitary adenoma (Cushing disease); paraneoplastic ACTH secretion (eg, small cell lung cancer, bronchial carcinoids)→ bilateral adrenal hyperplasia. Cushing disease is responsible for the majority of endogenous cases of Cushing syndrome.

**FINDINGS**

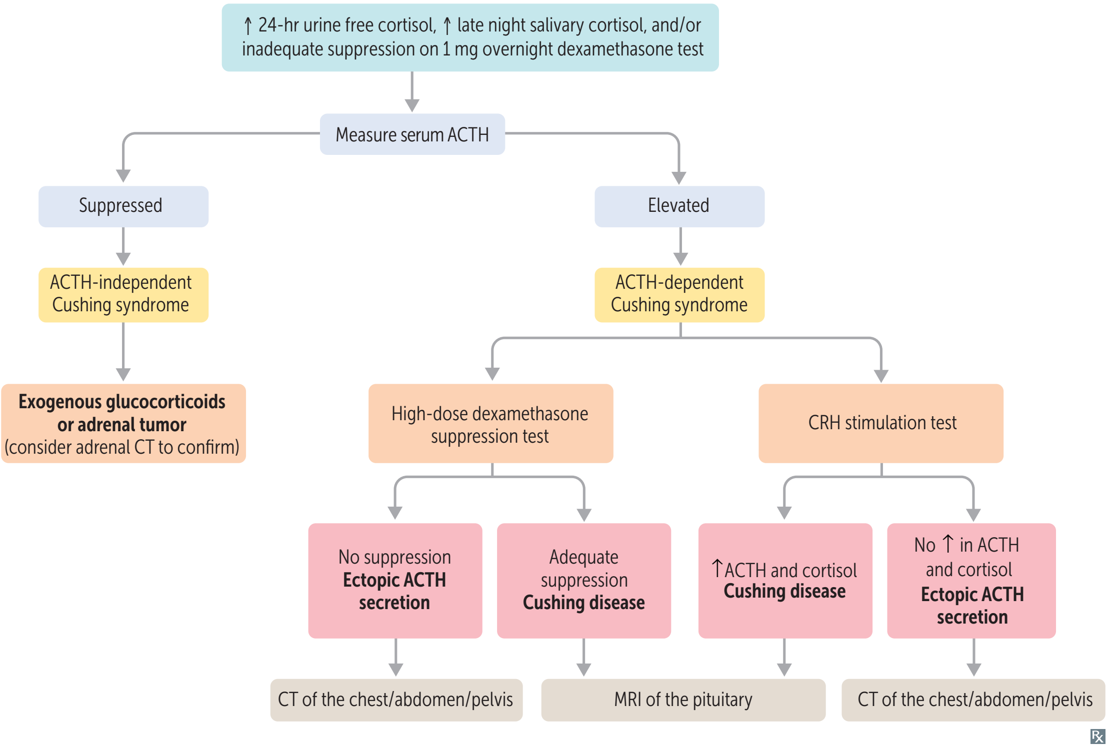
**CUSHING S**yndrome: ↑ **C**holesterol, ↑ **U**rinary free cortisol, **S**kin changes (thinning, striae A), **H**ypertension, **I**mmunosuppression, **N**eoplasm (a cause, not a finding), **G**rowth restriction (in children), ↑ **S**ugar (hyperglycemia, insulin resistance). Also, amenorrhea, moon facies B, buffalo hump, osteoporosis, ↑ weight (truncal obesity), hirsutism.

**DIAGNOSIS**

Screening tests include: ↑ free cortisol on 24-hr urinalysis, ↑ late night salivary cortisol, and no suppression with overnight low-dose dexamethasone test.







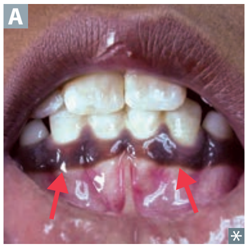
**Nelson syndrome**

Enlargement of pre-existing ACTH–secreting pituitary adenoma after bilateral adrenalectomy for refractory Cushing disease → ↑ ACTH (hyperpigmentation), mass effect (headaches, bitemporal hemianopia).
Treatment: transsphenoidal resection, postoperative pituitary irradiation for residual tumor.

**Adrenal insufficiency**

Inability of adrenal glands to generate enough glucocorticoids +/– mineralocorticoids for the body's needs. Can be acute or chronic. Symptoms include weakness, fatigue, orthostatic hypotension, muscle aches, weight loss, GI disturbances, sugar and/or salt cravings.
Treatment: glucocorticoid +/– mineralocorticoid replacement.

**Primary adrenal insufficiency**



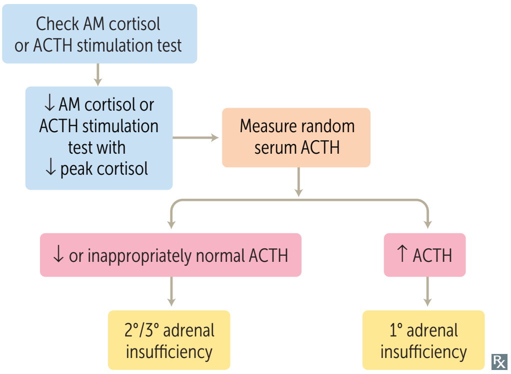

↓ gland function → ↓ cortisol, ↓ aldosterone → hypotension (hyponatremic volume contraction), hyperkalemia, metabolic acidosis, skin/mucosal hyperpigmentation A (↑ melanin synthesis due to ↑ MSH, a byproduct of POMC cleavage). **P**rimary **p**igments the skin/mucosa.
Addison disease—chronic 1° adrenal insufficiency; caused by adrenal atrophy or destruction. Most commonly due to autoimmune adrenalitis (developed world) or TB (developing world).

**Secondary and tertiary adrenal insufficiency**

↓ pituitary ACTH secretion (secondary) or ↓ hypothalamic CRH secretion (tertiary). No hyperkalemia (aldosterone synthesis preserved due to functioning adrenal gland, intact RAAS), no hyperpigmentation.
2° adrenal insufficiency is due to pituitary pathologies, 3° adrenal insufficiency is most commonly due to abrupt cessation of chronic steroid therapy (HPA suppression). **T**ertiary from **t**reatment.

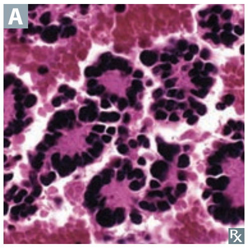
**Acute adrenal insufficiency**

Also called adrenal (addisonian) crisis; often precipitated by acute stressors that ↑ steroid requirements (eg, infection) in patients with pre-existing adrenal insufficiency or on steroid therapy. May present with acute abdomen, nausea, vomiting, altered mental status, shock.
Waterhouse-Friderichsen syndrome—bilateral adrenal hemorrhage often due to meningococcemia. May present with acute adrenal insufficiency, fever, petechiae, sepsis.

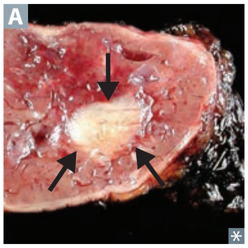


| | |
|---|---|
| **Hyperaldosteronism** | Increased secretion of aldosterone from adrenal gland. Clinical features include hypertension, ↓ or normal $K^+$, metabolic alkalosis. 1° hyperaldosteronism does not directly cause edema due to aldosterone escape mechanism. However, certain 2° causes of hyperaldosteronism (eg, heart failure) impair the aldosterone escape mechanism, leading to worsening of edema. |
| **Primary hyperaldosteronism** | Seen in patients with bilateral adrenal hyperplasia or adrenal adenoma (Conn syndrome). ↑ aldosterone, ↓ renin. Leads to treatment-resistant hypertension. |
| **Secondary hyperaldosteronism** | Seen in patients with renovascular hypertension, juxtaglomerular cell tumors (renin-producing), and edema (eg, cirrhosis, heart failure, nephrotic syndrome). |

| | |
|---|---|
| **Neuroendocrine tumors** | Heterogeneous group of neoplasms originating from neuroendocrine cells (which have traits similar to nerve cells and hormone-producing cells).<br>Most neoplasms occur in the GI system (eg, carcinoid, gastrinoma), pancreas (eg, insulinoma, glucagonoma), and lungs (eg, small cell carcinoma). Also in thyroid (eg, medullary carcinoma) and adrenals (eg, pheochromocytoma).<br>Neuroendocrine cells (eg, pancreatic β cells, enterochromaffin cells) share a common biologic function through amine precursor uptake decarboxylase (APUD) despite differences in embryologic origin, anatomic site, and secretory products (eg, chromogranin A, neuron-specific enolase [NSE], synaptophysin, serotonin, histamine, calcitonin). Treatment: surgical resection, somatostatin analogs. |

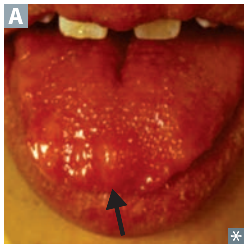
| | |
|---|---|
| **Neuroblastoma**<br> | Most common tumor of the adrenal medulla in **children,** usually < 4 years old. Originates from **n**eural crest cells. Occurs anywhere along the sympathetic chain.<br>Most common presentation is abdominal distension and a firm, irregular mass that can cross the midline (vs Wilms tumor, which is smooth and unilateral). Less likely to develop hypertension than with pheochromocytoma (**n**euroblastoma is **n**ormotensive). Can also present with opsoclonus-myoclonus syndrome ("dancing eyes-dancing feet").<br>↑ HVA and VMA (catecholamine metabolites) in urine. Homer-Wright rosettes (neuroblasts surrounding a central lumen A) characteristic of neuroblastoma and medulloblastoma. Bombesin and **N**SE ⊕. Associated with amplification of **N**-*myc* oncogene. |

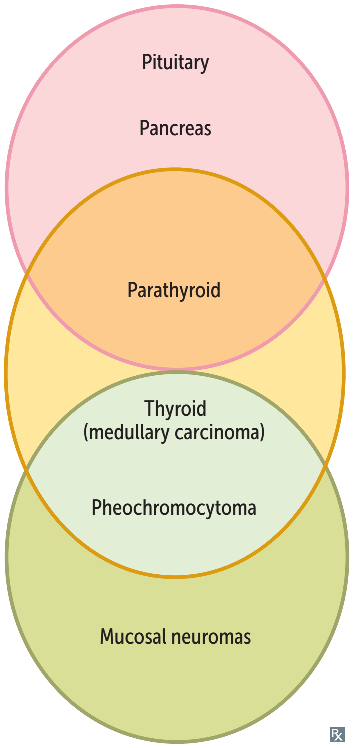
## Pheochromocytoma

| | | |
|---|---|---|
| ETIOLOGY  | Most common tumor of the adrenal medulla in **adults** A. Derived from chromaffin cells (arise from neural crest).<br>May be associated with germline mutations (eg, *NF-1*, *VHL*, *RET* [MEN 2A, 2B]). | **Rule of 10**'s:<br>10% malignant<br>10% bilateral<br>10% extra-adrenal (eg, bladder wall, organ of Zuckerkandl)<br>10% calcify<br>10% kids |
| SYMPTOMS | Most tumors secrete epinephrine, norepinephrine, and dopamine, which can cause episodic hypertension. May also secrete EPO → polycythemia.<br>Symptoms occur in "spells"—relapse and remit. | Episodic hyperadrenergic symptoms (**5 P**'s):<br>Pressure (↑ BP)<br>Pain (headache)<br>Perspiration<br>Palpitations (tachycardia)<br>Pallor |
| FINDINGS | ↑ catecholamines and metanephrines (eg, homovanillic acid, vanillylmandelic acid) in urine and plasma. | Chromogranin, synaptophysin and NSE ⊕. |
| TREATMENT | Irreversible α-antagonists (eg, phenoxybenzamine) followed by β-blockers prior to tumor resection. α-blockade must be achieved before giving β-blockers to avoid a hypertensive crisis. **A** before **B**. | **Phe**noxybenzamine for **phe**ochromocytoma. |

**Multiple endocrine neoplasias**

All **MEN** syndromes have autosomal **dominant** inheritance.
The X-**MEN** are **dominant** over villains.

| SUBTYPE | CHARACTERISTICS | COMMENTS |
|---|---|---|
| **MEN 1** | **P**ituitary tumors (prolactin or GH)<br>**P**ancreatic endocrine tumors—Zollinger-Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare)<br>**P**arathyroid adenomas<br>Associated with mutation of *MEN1* (menin, a tumor suppressor, chromosome 11), angiofibromas, collagenomas, meningiomas | |
| **MEN 2A** | **P**arathyroid hyperplasia<br>Medullary thyroid carcinoma—neoplasm of parafollicular C cells; secretes calcitonin; prophylactic thyroidectomy required<br>**P**heochromocytoma (secretes catecholamines)<br>Associated with mutation in *RET* (codes for receptor tyrosine kinase) | |
| **MEN 2B**  | Medullary thyroid carcinoma<br>**P**heochromocytoma<br>Mucosal neuromas **A** (oral/intestinal ganglioneuromatosis)<br>Associated with marfanoid habitus; mutation in *RET* gene | |

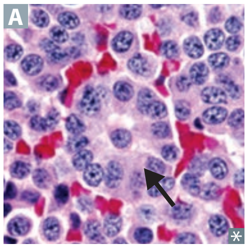



MEN 1 = 3 **P**'s: **p**ituitary, **p**arathyroid, and **p**ancreas
MEN 2A = 2 **P**'s: **p**arathyroid and **p**heochromocytoma
MEN 2B = 1 **P**: **p**heochromocytoma

## Pancreatic islet cell tumors

| | |
|---|---|
| **Insulinoma** | Tumor of pancreatic β cells → overproduction of insulin → hypoglycemia.<br>May see Whipple triad: low blood glucose, symptoms of hypoglycemia (eg, lethargy, syncope, diplopia), and resolution of symptoms after normalization of plasma glucose levels. Symptomatic patients have ↓ blood glucose and ↑ C-peptide levels (vs exogenous insulin use). ~ 10% of cases associated with MEN 1 syndrome.<br>Treatment: surgical resection. |
| **Glucagonoma** | Tumor of pancreatic α cells → overproduction of glucagon.<br>Presents with 6 D's: dermatitis (necrolytic migratory erythema), diabetes (hyperglycemia), DVT, declining weight, depression, diarrhea.<br>Treatment: octreotide, surgical resection. |
| **Somatostatinoma** | Tumor of pancreatic δ cells → overproduction of somatostatin → ↓ secretion of secretin, cholecystokinin, glucagon, insulin, gastrin, gastric inhibitory peptide (GIP).<br>May present with diabetes/glucose intolerance, steatorrhea, gallstones, achlorhydria.<br>Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control. |

## Carcinoid tumors




Carcinoid tumors arise from neuroendocrine cells, most commonly in the intestine or lung. Neuroendocrine cells secrete 5-HT, which undergoes hepatic first-pass metabolism and enzymatic breakdown by MAO in the lung. If 5-HT reaches the systemic circulation (eg, after liver metastasis), carcinoid tumor may present with **carcinoid syndrome**—episodic flushing, diarrhea, wheezing, right-sided valvular heart disease (eg, tricuspid regurgitation, pulmonic stenosis), niacin deficiency (pellagra).

Histology: prominent rosettes (arrow in A), chromogranin A ⊕, synaptophysin ⊕.

Treatment: surgical resection, somatostatin analog (eg, octreotide) or tryptophan hydroxylase inhibitor (eg, telotristat) for symptom control.

Rule of thirds:
- 1/3 metastasize
- 1/3 present with 2nd malignancy
- 1/3 are multiple

## Zollinger-Ellison syndrome

Gastrin-secreting tumor (gastrinoma) of duodenum or pancreas. Acid hypersecretion causes recurrent ulcers in duodenum and jejunum. Presents with abdominal pain (peptic ulcer disease, distal ulcers), diarrhea (malabsorption). Positive secretin stimulation test: ↑ gastrin levels after administration of secretin, which normally inhibits gastrin release. May be associated with MEN 1.

## ▸ ENDOCRINE—PHARMACOLOGY

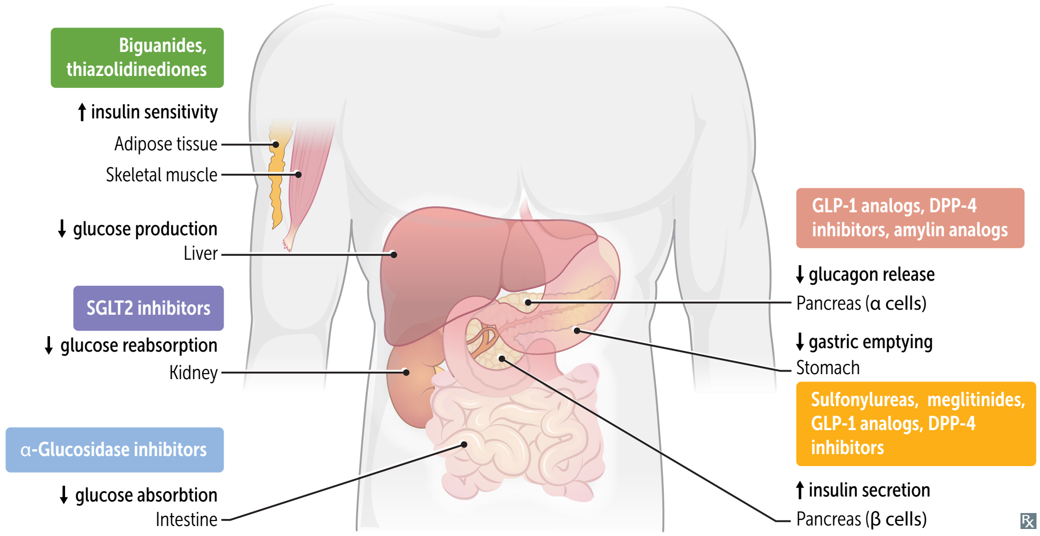
### Diabetes mellitus therapy

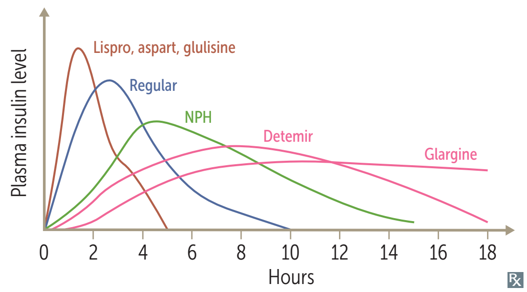
All patients with diabetes mellitus should receive education on diet, exercise, blood glucose monitoring, and complication management. Treatment differs based on the type of diabetes and glycemic control:

- Type 1 DM—insulin replacement
- Type 2 DM—oral agents (metformin is first line), non-insulin injectables, insulin replacement; weight loss particularly helpful in lowering blood glucose
- Gestational DM—insulin replacement if nutrition therapy and exercise alone fail

Regular (short-acting) insulin is preferred for DKA (IV), hyperkalemia (+ glucose), stress hyperglycemia.

These drugs help **T**o **n**ormalize **p**ancreatic **f**unction ( -gli**t**s, -gli**n**s, -gli**p**s, -gli**f**s).




| DRUG CLASS | MECHANISM | ADVERSE EFFECTS |
|---|---|---|
| **Insulin preparations** | | |
| Rapid acting (1-hr peak): **L**ispro, **A**spart, **G**lulisine (no **LAG**)<br>Short acting (2–3 hr peak): regular<br>Intermediate acting (4–10 hr peak): NPH<br>Long acting (no real peak): detemir, glargine | Bind insulin receptor (tyrosine kinase activity)<br>Liver: ↑ glucose storage as glycogen<br>Muscle: ↑ glycogen, protein synthesis<br>Fat: ↑ TG storage<br>Cell membrane: ↑ $K^+$ uptake | Hypoglycemia, lipodystrophy, hypersensitivity reactions (rare), weight gain<br> |

**Diabetes mellitus therapy *(continued)***

| DRUG CLASS | MECHANISM | ADVERSE EFFECTS |
|---|---|---|
| **Increase insulin sensitivity** | | |
| **Biguanides**<br>Metformin | Inhibit mGPD → inhibition of hepatic gluconeogenesis and the action of glucagon.<br>↑ glycolysis, peripheral glucose uptake (↑ insulin sensitivity). | GI upset, lactic acidosis (use with caution in renal insufficiency), vitamin $B_{12}$ deficiency.<br>Weight loss (often desired). |
| **Thiazolidinediones**<br>"-glits"<br>Pioglitazone, rosiglitazone | Activate PPAR-γ (a nuclear receptor) → ↑ insulin sensitivity and levels of adiponectin → regulation of glucose metabolism and fatty acid storage. | Weight gain, edema, HF, ↑ risk of fractures.<br>Delayed onset of action (several weeks).<br>Rosiglitazone: ↑ risk of MI, cardiovascular death. |
| **Increase insulin secretion** | | |
| **Sulfonylureas (1st gen)**<br>Chlorpropamide, tolbutamide | Close $K^+$ channels in pancreatic B cell membrane → cell depolarizes → insulin release via ↑ $Ca^{2+}$ influx. | Disulfiram-like reaction with first-generation sulfonylureas only (rarely used). |
| **Sulfonylureas (2nd gen)**<br>Glipizide, glyburide | | Hypoglycemia (↑ risk in renal insufficiency), weight gain. |
| **Meglitinides**<br>"-glins"<br>Nateglinide, repaglinide | | |
| **Increase glucose-induced insulin secretion** | | |
| **GLP-1 analogs**<br>Exenatide, liraglutide | ↓ glucagon release, ↓ gastric emptying, ↑ glucose-dependent insulin release. | Nausea, vomiting, pancreatitis. Weight loss (often desired).<br>↑ satiety (often desired). |
| **DPP-4 inhibitors**<br>"-glips"<br>Linagliptin, saxagliptin, sitagliptin | Inhibit DPP-4 enzyme that deactivates GLP-1 → ↓ glucagon release, ↓ gastric emptying.<br>↑ glucose-dependent insulin release. | Respiratory and urinary infections, weight neutral.<br>↑ satiety (often desired). |
| **Decrease glucose absorption** | | |
| **Sodium-glucose co-transporter 2 inhibitors**<br>"-glifs"<br>Canagliflozin, dapagliflozin, empagliflozin | Block reabsorption of glucose in proximal convoluted tubule. | Glucosuria (UTIs, vulvovaginal candidiasis), dehydration (orthostatic hypotension), weight loss.<br>Use with caution in renal insufficiency (↓ efficacy with ↓ GFR). |
| **α-glucosidase inhibitors**<br>Acarbose, miglitol | Inhibit intestinal brush-border α-glucosidases → delayed carbohydrate hydrolysis and glucose absorption → ↓ postprandial hyperglycemia. | GI upset, bloating.<br>Not recommended in renal insufficiency. |
| **Others** | | |
| **Amylin analogs**<br>Pramlintide | ↓ glucagon release, ↓ gastric emptying. | Hypoglycemia, nausea. ↑ satiety (often desired). |

## Thionamides

Propylthiouracil, methimazole.

| | |
|---|---|
| MECHANISM | Block thyroid peroxidase, inhibiting the oxidation of iodide as well as the organification and coupling of iodine → inhibition of thyroid hormone synthesis. **P**TU also blocks 5′-deiodinase → ↓ **P**eripheral conversion of $T_4$ to $T_3$. |
| CLINICAL USE | Hyperthyroidism. **P**TU used in **P**rimary (first) trimester of pregnancy (due to methimazole teratogenicity); methimazole used in second and third trimesters of pregnancy (due to risk of PTU-induced hepatotoxicity). Not used to treat Graves ophthalmopathy (treated with corticosteroids). |
| ADVERSE EFFECTS | Skin rash, agranulocytosis (rare), aplastic anemia, hepatotoxicity.<br>PTU use has been associated with ANCA-positive vasculitis.<br>Methimazole is a possible teratogen (can cause aplasia cutis). |

## Levothyroxine, liothyronine

| | |
|---|---|
| MECHANISM | Hormone replacement for $T_4$ (levothyroxine) or $T_3$ (liothyronine). |
| CLINICAL USE | Hypothyroidism, myxedema. May be abused for weight loss. Distinguish exogenous hyperthyroidism from endogenous hyperthyroidism by using a combination of TSH receptor antibodies, radioactive iodine uptake, and/or measurement of thyroid blood flow on ultrasound. |
| ADVERSE EFFECTS | Tachycardia, heat intolerance, tremors, arrhythmias. |

## Hypothalamic/pituitary drugs

| DRUG | CLINICAL USE |
|---|---|
| Conivaptan, tolvaptan | ADH antagonists<br>SIADH (block action of ADH at $V_2$-receptor) |
| Demeclocycline | Interferes with ADH signaling, a tetracycline<br>SIADH |
| Desmopressin | ADH analog<br>Central DI, von Willebrand disease, sleep enuresis, hemophilia A |
| GH | GH deficiency, Turner syndrome |
| Oxytocin | Induction of labor (stimulates uterine contractions), control uterine hemorrhage |
| Somatostatin (octreotide) | Acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, esophageal varices |

## Fludrocortisone

| | |
|---|---|
| MECHANISM | Synthetic analog of aldosterone with glucocorticoid effects. **Fluid**rocortisone retains **fluid**. |
| CLINICAL USE | Mineralocorticoid replacement in 1° adrenal insufficiency. |
| ADVERSE EFFECTS | Similar to glucocorticoids; also edema, exacerbation of heart failure, hyperpigmentation. |

## Cinacalcet

| | |
|---|---|
| MECHANISM | **Sen**sitizes **calc**ium-sensing receptor (CaSR) in parathyroid gland to circulating $Ca^{2+}$ → ↓ PTH. Pronounce "**Sen**a**calc**et." |
| CLINICAL USE | 2° hyperparathyroidism in patients with CKD receiving hemodialysis, hypercalcemia in 1° hyperparathyroidism (if parathyroidectomy fails), or in parathyroid carcinoma. |
| ADVERSE EFFECTS | Hypocalcemia. |

## Sevelamer

| | |
|---|---|
| MECHANISM | Nonabsorbable phosphate binder that prevents phosphate absorption from the GI tract. |
| CLINICAL USE | Hyperphosphatemia in CKD. |
| ADVERSE EFFECTS | Hypophosphatemia, GI upset. |

## Cation exchange resins

Patiromer, sodium polystyrene sulfonate, zirconium cyclosilicate.

| | |
|---|---|
| MECHANISM | Bind $K^+$ in colon in exchange for other cations (eg, $Na^+$, $Ca^{2+}$) → $K^+$ excreted in feces. |
| CLINICAL USE | Hyperkalemia. |
| ADVERSE EFFECTS | Hypokalemia, GI upset. |

▶ NOTES

# Gastrointestinal

*"A good set of bowels is worth more to a man than any quantity of brains."*

—Josh Billings

*"Man should strive to have his intestines relaxed all the days of his life."*

—Moses Maimonides

*"All right, let's not panic. I'll make the money by selling one of my livers. I can get by with one."*

—Homer Simpson, *The Simpsons*

*"The truth does not change according to our ability to stomach it emotionally."*

—Flannery O'Connor

When studying the gastrointestinal system, be sure to understand the normal embryology, anatomy, and physiology and how the system is affected by various pathologies. Study not only disease pathophysiology, but also its specific findings, so that you can differentiate between two similar diseases. For example, what specifically makes ulcerative colitis different from Crohn disease? Also, be comfortable with basic interpretation of abdominal x-rays, CT scans, and endoscopic images.

## ▸ GASTROINTESTINAL—EMBRYOLOGY

### Normal gastrointestinal embryology

Foregut—esophagus to duodenum at level of pancreatic duct and common bile duct insertion (ampulla of Vater).
Midgut—lower duodenum to proximal 2/3 of transverse colon.
Hindgut—distal 1/3 of transverse colon to anal canal above pectinate line.
Midgut:
- 6th week of development—physiologic herniation of midgut through umbilical ring
- 10th week of development—returns to abdominal cavity + rotates around superior mesenteric artery (SMA), total 270° counterclockwise

### Ventral wall defects

Developmental defects due to failure of rostral fold closure (eg, sternal defects [ectopia cordis]), lateral fold closure (eg, omphalocele, gastroschisis), or caudal fold closure (eg, bladder exstrophy).

| | Gastroschisis | Omphalocele |
|---|---|---|
| ETIOLOGY | Extrusion of abdominal contents through abdominal folds (typically right of umbilicus) | Failure of lateral walls to migrate at umbilical ring → persistent midline herniation of abdominal contents into umbilical cord |
| COVERAGE | Not covered by peritoneum or amnion A; "the guts come out of the gap (schism) in the letter G" | Covered by peritoneum and amnion B (light gray shiny sac); "abdominal contents are sealed in the letter O" |
| ASSOCIATIONS | Not associated with chromosome abnormalities; favorable prognosis | Associated with congenital anomalies (eg, trisomies 13 and 18, Beckwith-Wiedemann syndrome) and other structural abnormalities (eg, cardiac, GU, neural tube) |



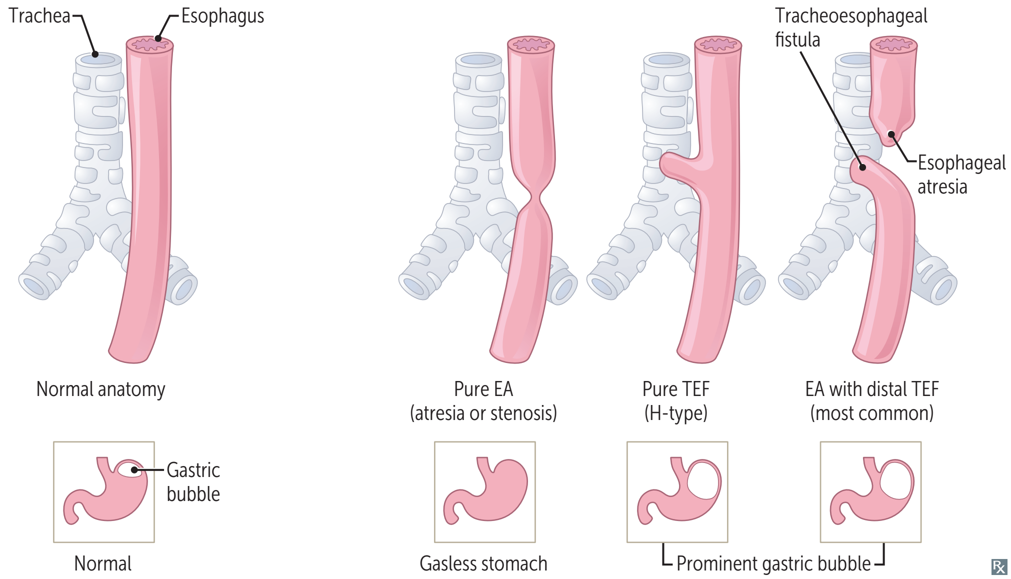
### Congenital umbilical hernia


Failure of umbilical ring to close after physiologic herniation of midgut. Covered by skin C. Protrudes with ↑ intra-abdominal pressure (eg, crying). May be associated with congenital disorders (eg, Down syndrome, congenital hypothyroidism). Small defects usually close spontaneously.

**Tracheoesophageal anomalies**

Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF) is the most common (85%) and often presents as polyhydramnios in utero (due to inability of fetus to swallow amniotic fluid). Neonates drool, choke, and vomit with first feeding. TEFs allow air to enter stomach (visible on CXR). Cyanosis is 2° to laryngospasm (to avoid reflux-related aspiration). Clinical test: failure to pass nasogastric tube into stomach.

In **H**-type, the fistula resembles the letter **H**. In pure EA, CXR shows gasless abdomen.

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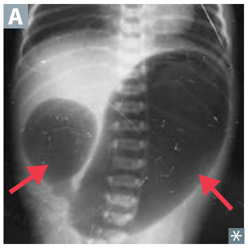
**Intestinal atresia**




Presents with bilious vomiting and abdominal distension within first 1–2 days of life.

**Duodenal atresia**—failure to recanalize. X-ray A shows "**d**ouble bubble" (dilated stomach, proximal duodenum). Associated with **D**own syndrome.

**Jejunal and ileal atresia**—disruption of mesenteric vessels (typically SMA) → ischemic necrosis of fetal intestine → segmental resorption: bowel becomes discontinuous. X-ray may show "triple bubble" (dilated stomach, duodenum, proximal jejunum) and gasless colon.

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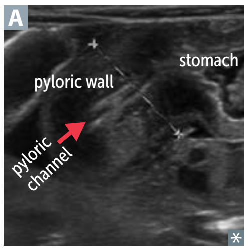
**Hypertrophic pyloric stenosis**



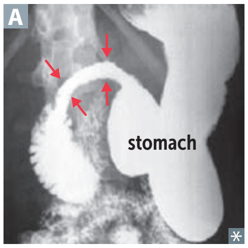

Most common cause of gastric outlet obstruction in infants (1:600). Palpable olive-shaped mass in epigastric region, visible peristaltic waves, and nonbilious projectile vomiting at ~ 2–6 weeks old. More common in firstborn males; associated with exposure to macrolides.

Results in hypokalemic hypochloremic metabolic alkalosis (2° to vomiting of gastric acid and subsequent volume contraction).

Ultrasound shows thickened and lengthened pylorus A.

Treatment: surgical incision of pyloric muscles (pyloromyotomy).

### Pancreas and spleen embryology

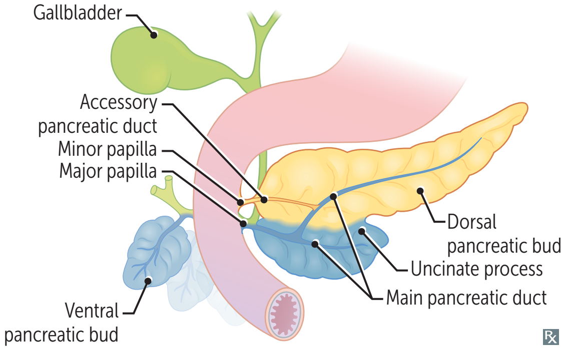



Pancreas—derived from foregut. Ventral pancreatic bud contributes to uncinate process and main pancreatic duct. The dorsal pancreatic bud alone becomes the body, tail, isthmus, and accessory pancreatic duct. Both the ventral and dorsal buds contribute to pancreatic head.

**Annular pancreas**—abnormal rotation of ventral pancreatic bud forms a ring of pancreatic tissue → encircles 2nd part of duodenum; may cause duodenal narrowing (arrows in A) and vomiting.

**Pancreas divisum**—ventral and dorsal parts fail to fuse at 7 weeks of development. Common anomaly; mostly asymptomatic, but may cause chronic abdominal pain and/or pancreatitis.

Spleen—arises in mesentery of stomach (hence is mesodermal) but has foregut supply (celiac trunk → splenic artery).

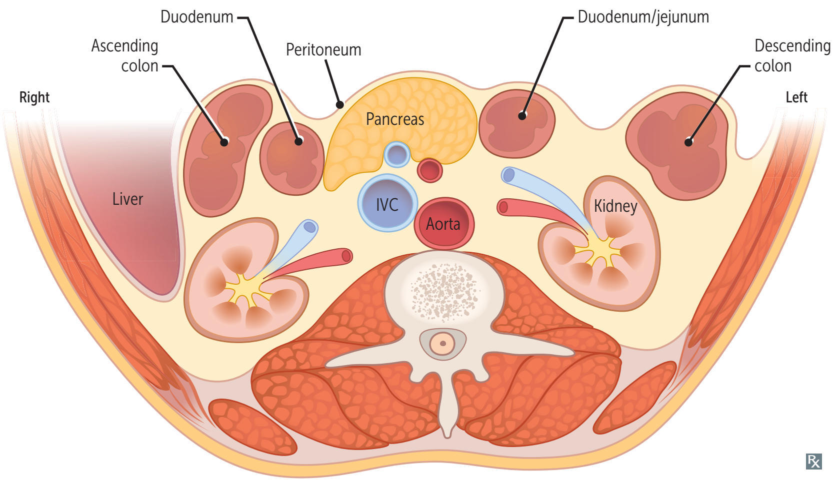


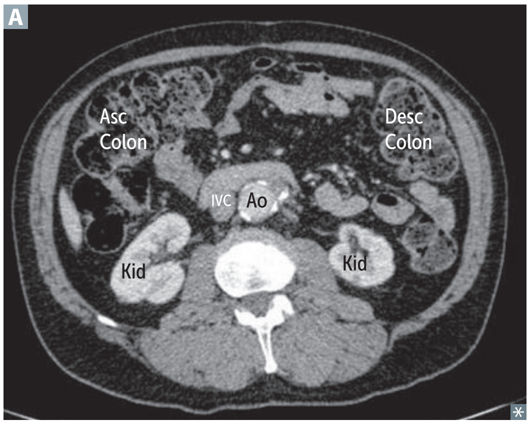

## ▸ GASTROINTESTINAL—ANATOMY

### Retroperitoneal structures

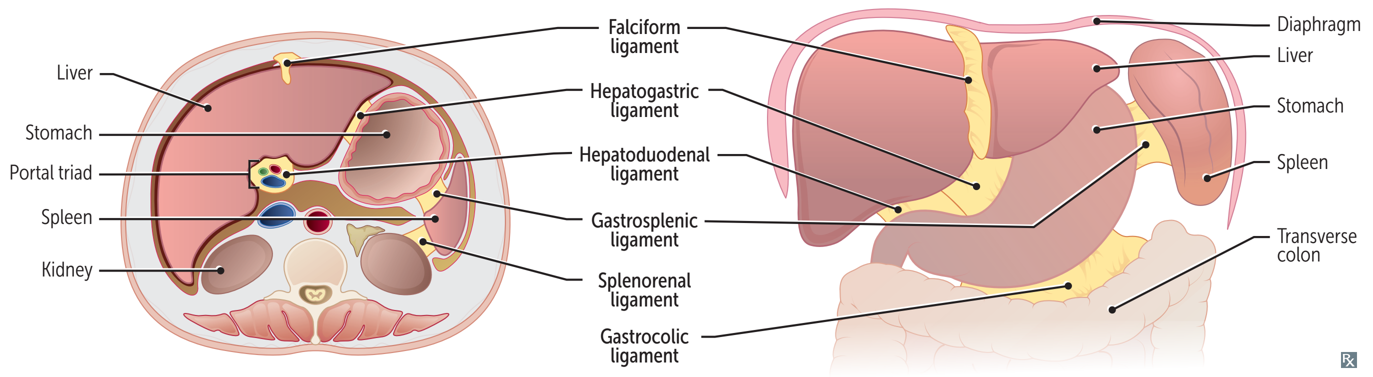
Retroperitoneal structures A are posterior to (and outside of) the peritoneal cavity. Injuries to retroperitoneal structures can cause blood or gas accumulation in retroperitoneal space.

SAD PUCKER:
- Suprarenal (adrenal) glands [not shown]
- Aorta and IVC
- Duodenum (2nd through 4th parts)
- Pancreas (except tail)
- Ureters [not shown]
- Colon (descending and ascending)
- Kidneys
- Esophagus (thoracic portion) [not shown]
- Rectum (partially) [not shown]



### Important gastrointestinal ligaments



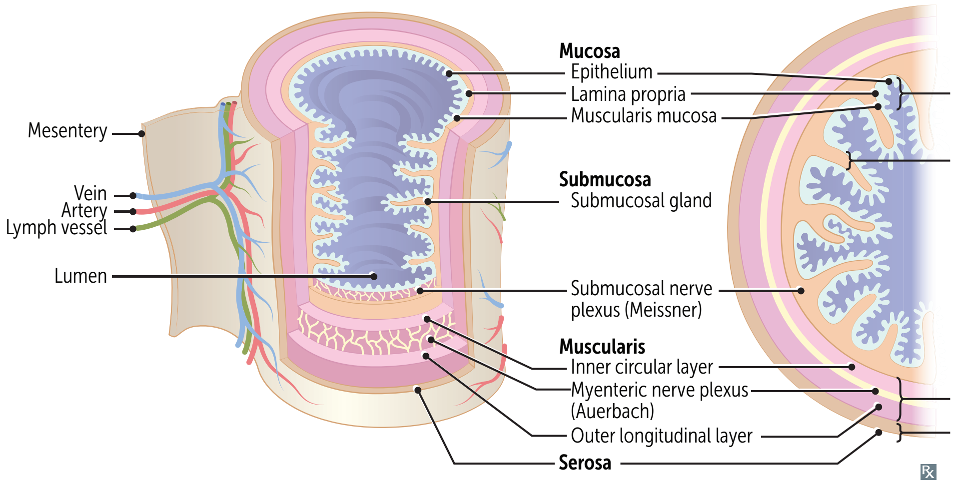

| LIGAMENT | CONNECTS | STRUCTURES CONTAINED | NOTES |
|---|---|---|---|
| **Falciform ligament** | Liver to anterior abdominal wall | Ligamentum teres hepatis (derivative of fetal umbilical vein), patent paraumbilical veins | Derivative of ventral mesentery |
| **Hepatoduodenal ligament** | Liver to duodenum | Portal triad: proper hepatic artery, portal vein, common bile duct | Derivative of ventral mesentery<br>Pringle maneuver—ligament is compressed manually or with a vascular clamp in omental foramen to control bleeding from hepatic inflow source<br>Borders the omental foramen, which connects the greater and lesser sacs<br>Part of lesser omentum |
| **Hepatogastric ligament** | Liver to lesser curvature of stomach | Gastric vessels | Derivative of ventral mesentery<br>Separates greater and lesser sacs on the right<br>May be cut during surgery to access lesser sac<br>Part of lesser omentum |
| **Gastrocolic ligament** | Greater curvature and transverse colon | Gastroepiploic arteries | Derivative of dorsal mesentery<br>Part of greater omentum |
| **Gastrosplenic ligament** | Greater curvature and spleen | Short gastrics, left gastroepiploic vessels | Derivative of dorsal mesentery<br>Separates greater and lesser sacs on the left<br>Part of greater omentum |
| **Splenorenal ligament** | Spleen to left pararenal space | Splenic artery and vein, tail of pancreas | Derivative of dorsal mesentery |

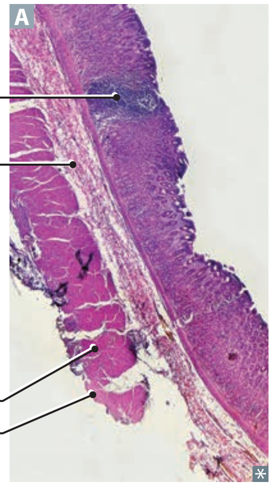
## Digestive tract anatomy

Layers of gut wall A (inside to outside—**MSMS**):
- **M**ucosa—epithelium, lamina propria, muscularis mucosa
- **S**ubmucosa—includes **s**ubmucosal nerve plexus (Mei**ss**ner), **s**ecretes fluid
- **M**uscularis externa—includes **m**yenteric nerve plexus (Auerbach), **m**otility
- **S**erosa (when intraperitoneal), adventitia (when retroperitoneal)

Ulcers can extend into submucosa, inner or outer muscular layer. Erosions are in mucosa only.

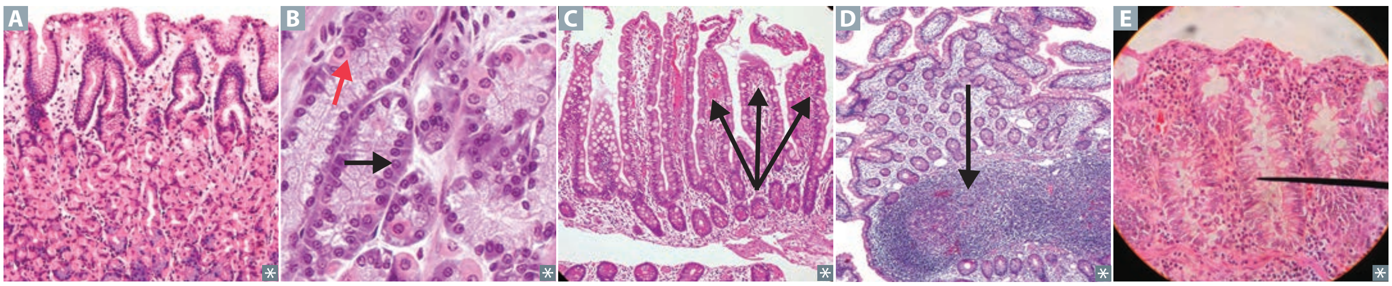
Frequency of basal electric rhythm (slow waves), which originate in the interstitial cells of Cajal: duodenum > ileum > stomach.



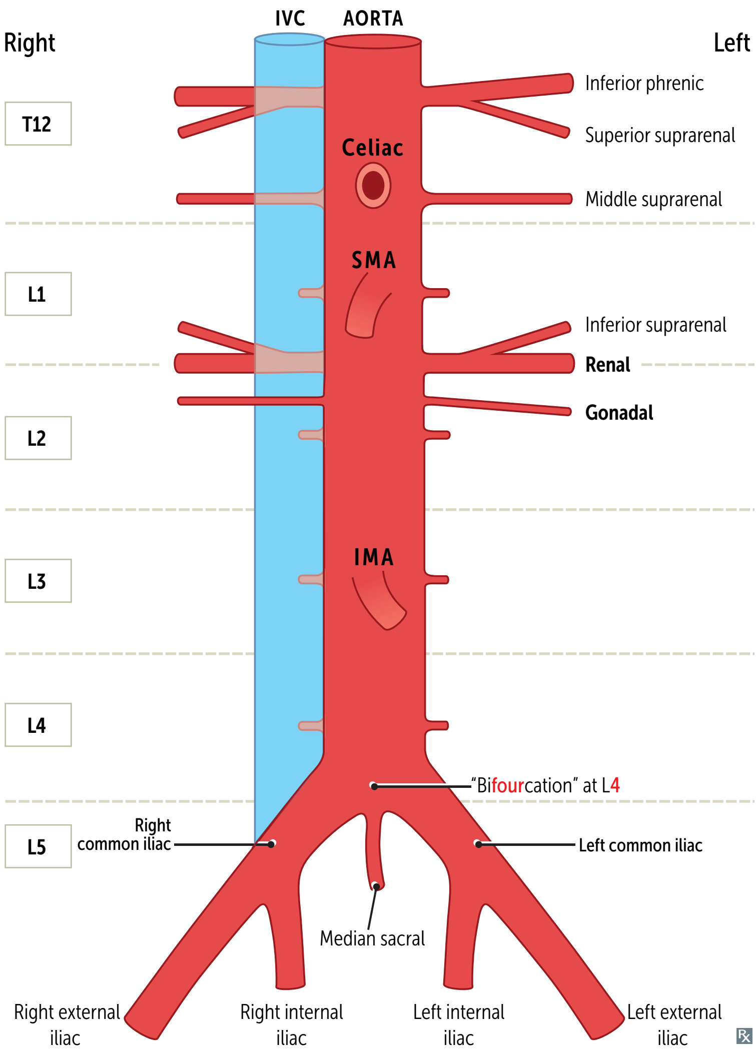




## Digestive tract histology

| | |
|---|---|
| **Esophagus** | Nonkeratinized stratified squamous epithelium. Upper 1/3, striated muscle; middle and lower 2/3 smooth muscle, with some overlap at the transition. |
| **Stomach** | Gastric glands A. **P**arietal cells are eosinophilic (**p**ink, red arrow in B), chief cells are basophilic (black arrow in B). |
| **Duodenum** | Villi and microvilli ↑ absorptive surface. **B**runner glands (**b**icarbonate-secreting cells of submucosa) and crypts of Lieberkühn (contain stem cells that replace enterocytes/goblet cells and Paneth cells that secrete defensins, lysozyme, and TNF). |
| **Jejunum** | Villi C, crypts of Lieberkühn, and plicae circulares (also present in distal duodenum). |
| **Ileum** | Villi, Peyer patches (arrow in D; lymphoid aggregates in lamina propria, submucosa), plicae circulares (proximal ileum), and crypts of Lieberkühn. Largest number of goblet cells in the small intestine. |
| **Colon** | Crypts of Lieberkühn with abundant goblet cells, but no villi E. |



## Abdominal aorta and branches




Arteries supplying GI structures are single and branch anteriorly.

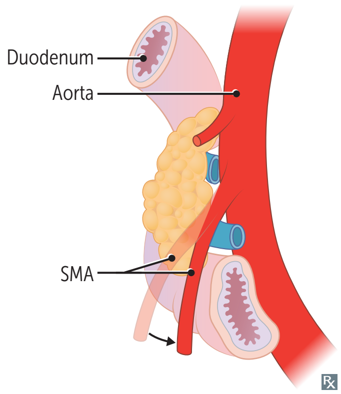
Arteries supplying non-GI structures are paired and branch laterally and posteriorly.

Two areas of the colon have dual blood supply from distal arterial branches ("watershed regions") → susceptible in colonic ischemia:

- Splenic flexure—SMA and IMA
- Rectosigmoid junction—the last sigmoid arterial branch from the IMA and superior rectal artery

**Nutcracker syndrome**—compression of left renal vein between superior mesenteric artery and aorta. May cause abdominal (flank) pain, gross hematuria (from rupture of thin-walled renal varicosities), left-sided varicocele.

**Superior mesenteric artery syndrome**—characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when SMA and aorta compress transverse (third) portion of duodenum. Typically occurs in conditions associated with diminished mesenteric fat (eg, low body weight/malnutrition).



### Gastrointestinal blood supply and innervation

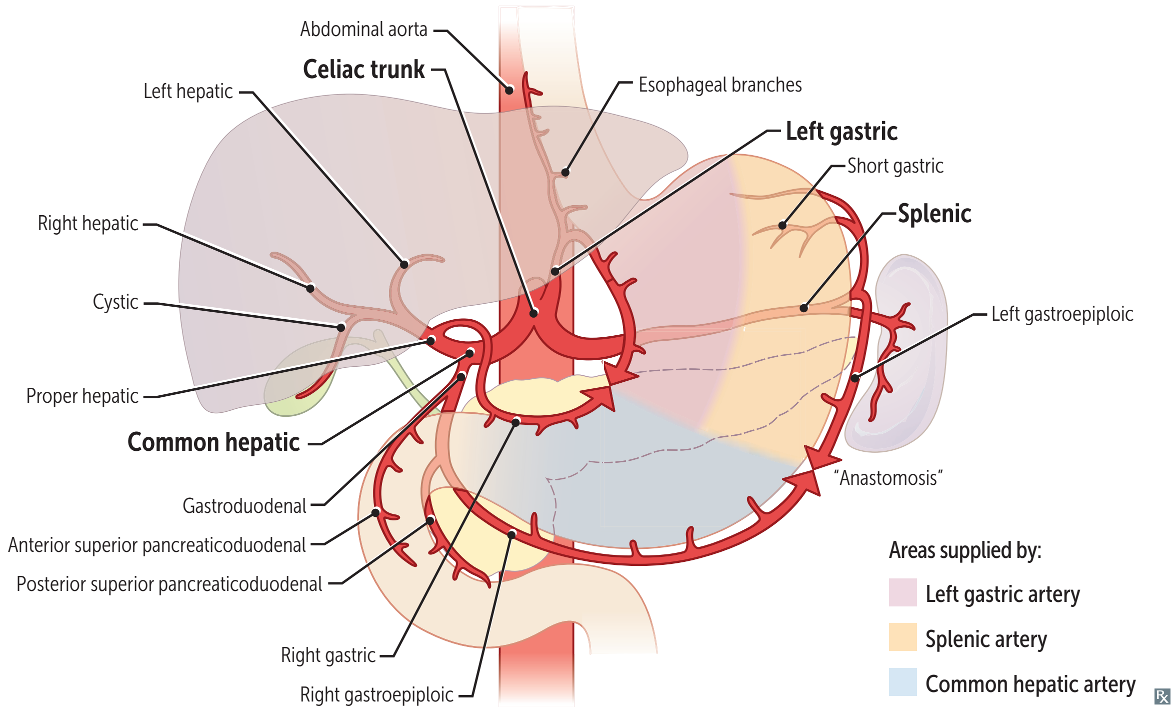
| EMBRYONIC GUT REGION | ARTERY | PARASYMPATHETIC INNERVATION | VERTEBRAL LEVEL | STRUCTURES SUPPLIED |
|---|---|---|---|---|
| **Foregut** | Celiac | Vagus | T12/L1 | Pharynx (vagus nerve only) and lower esophagus (celiac artery only) to proximal duodenum; liver, gallbladder, pancreas, spleen (mesoderm) |
| **Midgut** | SMA | Vagus | L1 | Distal duodenum to proximal 2/3 of transverse colon |
| **Hindgut** | IMA | Pelvic | L3 | Distal 1/3 of transverse colon to upper portion of anal canal |

### Celiac trunk

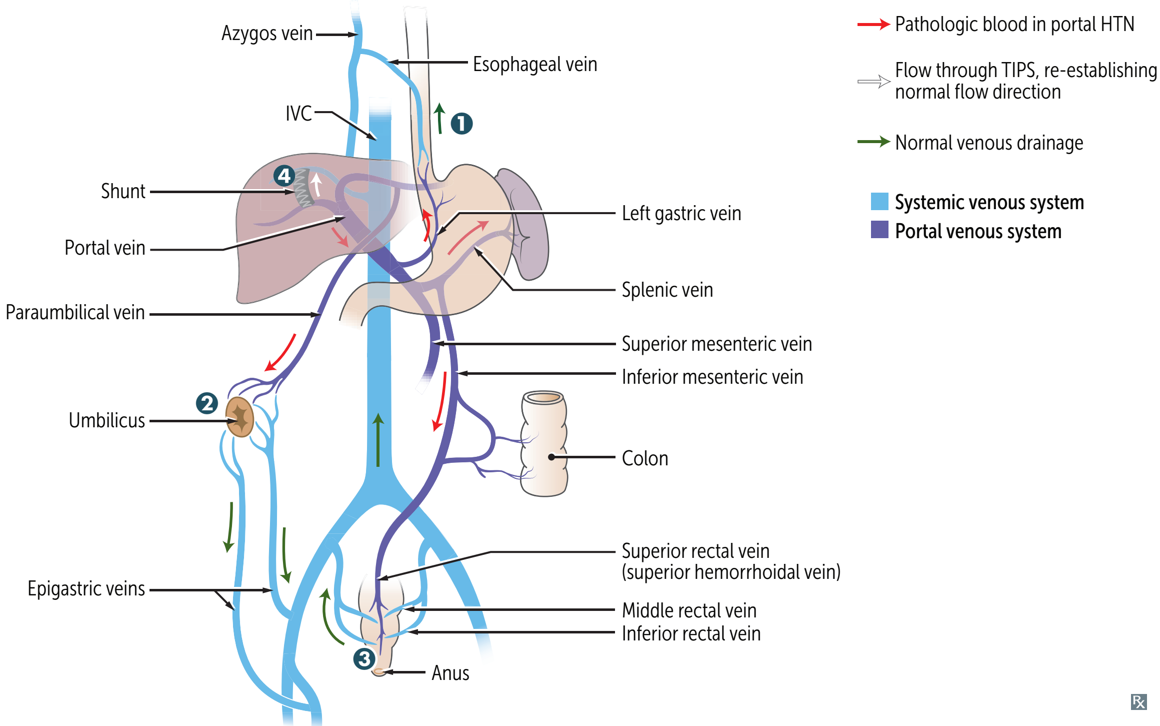
Branches of celiac trunk: common hepatic, splenic, and left gastric. These constitute the main blood supply of the foregut.

Strong anastomoses exist between:

- Left and right gastroepiploics
- Left and right gastrics



## Portosystemic anastomoses



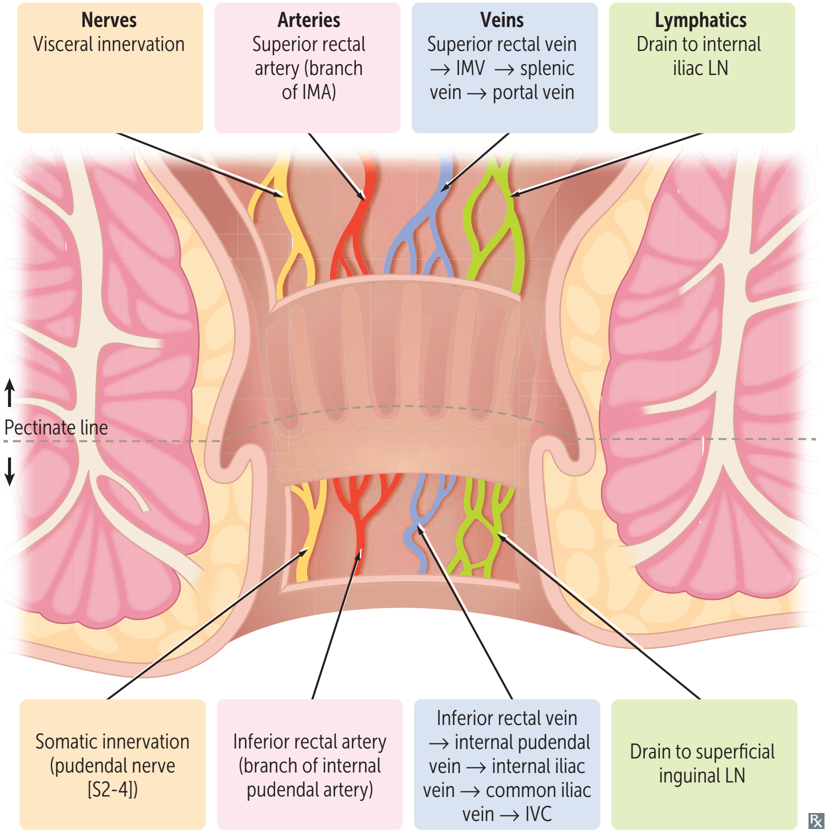

| SITE OF ANASTOMOSIS | CLINICAL SIGN | PORTAL ↔ SYSTEMIC |
|---|---|---|
| ❶ Esophagus | Esophageal varices | Left gastric ↔ esophageal (drains into azygos) |
| ❷ Umbilicus | Caput medusae | Paraumbilical ↔ small epigastric veins of the anterior abdominal wall. |
| ❸ Rectum | Anorectal varices | Superior rectal ↔ middle and inferior rectal |

Varices of **gut**, **butt**, and **caput** (medusae) are commonly seen with portal hypertension.

❹ Treatment with a **T**ransjugular **I**ntrahepatic **P**ortosystemic **S**hunt (**TIPS**) between the portal vein and hepatic vein relieves portal hypertension by shunting blood to the systemic circulation, bypassing the liver. TIPS can precipitate hepatic encephalopathy due to ↓ clearance of ammonia from shunting.

## Pectinate line

Also called dentate line. Formed where endoderm (hindgut) meets ectoderm.




**Above pectinate line:** internal hemorrhoids, adenocarcinoma.

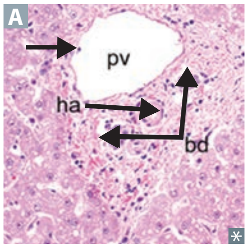
Internal hemorrhoids receive visceral innervation and are therefore **not painful**.

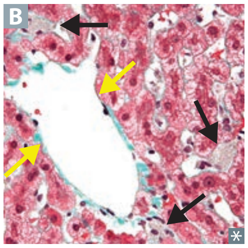
**Below pectinate line:** external hemorrhoids, anal fissures, squamous cell carcinoma.

External hemorrhoids receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore **painful** if thrombosed.

**Anal fissure**—tear in anoderm below pectinate line. Pain while pooping; blood on toilet paper. Located in the posterior midline because this area is poorly perfused. Associated with low-fiber diets and constipation.

## Liver tissue architecture




The functional unit of the liver is made up of hexagonally arranged lobules surrounding the central vein with portal triads on the edges (consisting of a portal vein, hepatic artery, bile ducts, as well as lymphatics) A.

Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids.

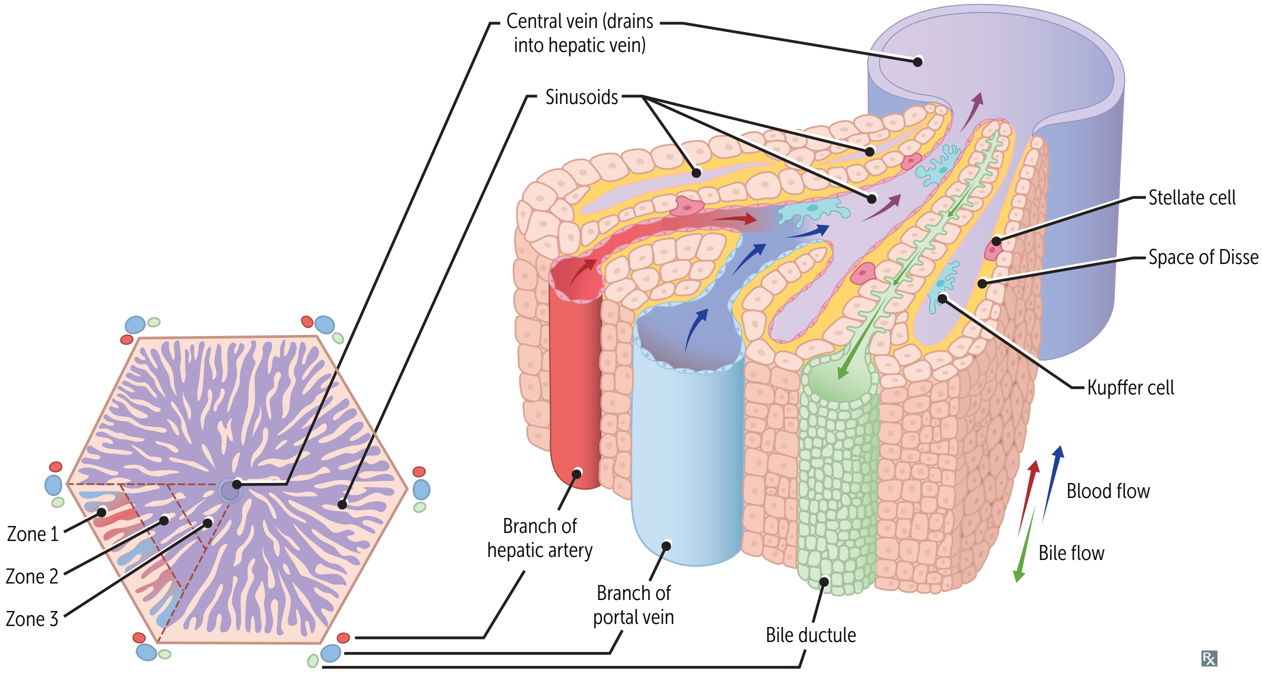
Kupffer cells (specialized macrophages) located in sinusoids (black arrows in B; yellow arrows show central vein) clear bacteria and damaged or senescent RBCs.

Hepatic stellate (Ito) cells in space of Disse store vitamin A (when quiescent) and produce extracellular matrix (when activated). Responsible for hepatic fibrosis.

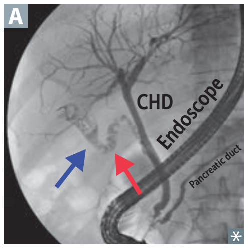
Zone I—periportal zone:
- Affected 1st by viral hepatitis
- Best oxygenated, most resistant to circulatory compromise
- Ingested toxins (eg, cocaine)

Zone II—intermediate zone:
- Yellow fever

Zone III—pericentral (centrilobular) zone:
- Affected 1st by ischemia (least oxygenated)
- High concentration of cytochrome P-450
- Most sensitive to metabolic toxins (eg, ethanol, $CCl_4$, halothane, rifampin, acetaminophen)
- Site of alcoholic hepatitis



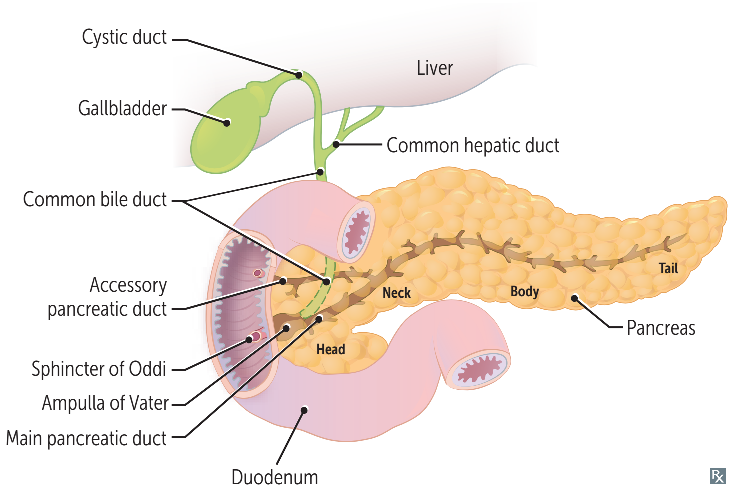
## Biliary structures




Cholangiography shows filling defects in gallbladder (blue arrow in A) and cystic duct (red arrow in A).

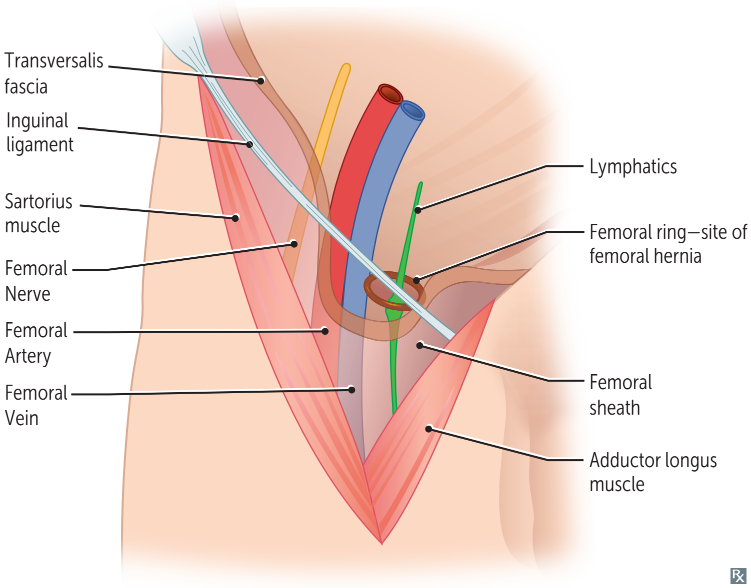
Gallstones that reach the confluence of the common bile and pancreatic ducts at the ampulla of Vater can block both the common bile and pancreatic ducts (double duct sign), causing both cholangitis and pancreatitis, respectively.

Tumors that arise in head of pancreas (usually ductal adenocarcinoma) can cause obstruction of common bile duct → enlarged gallbladder with painless jaundice (Courvoisier sign).

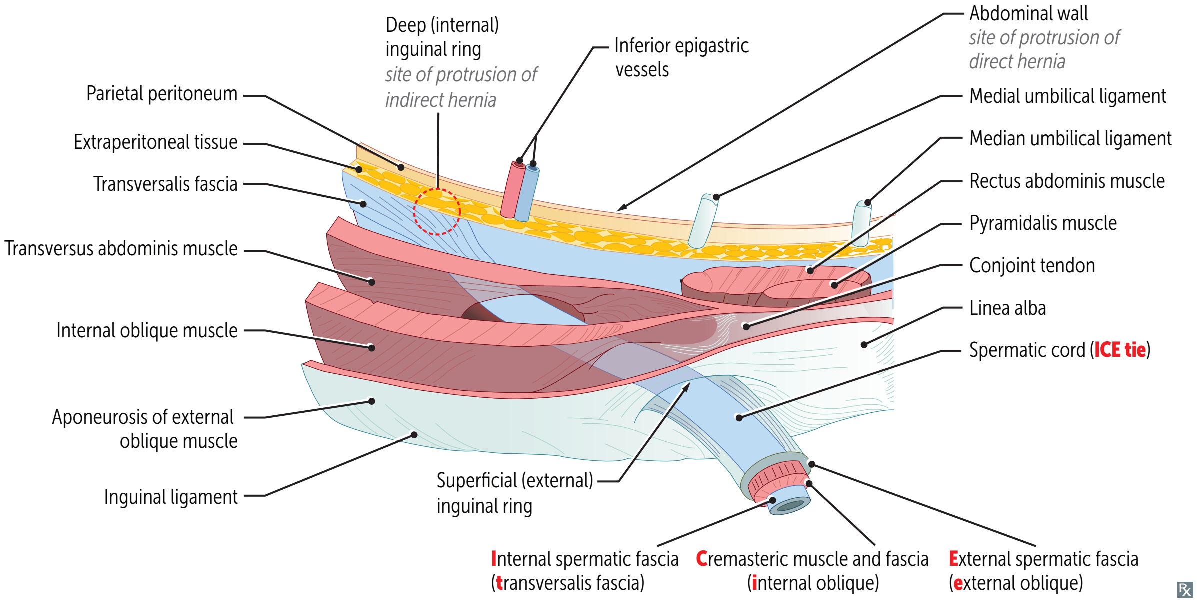



## Femoral region

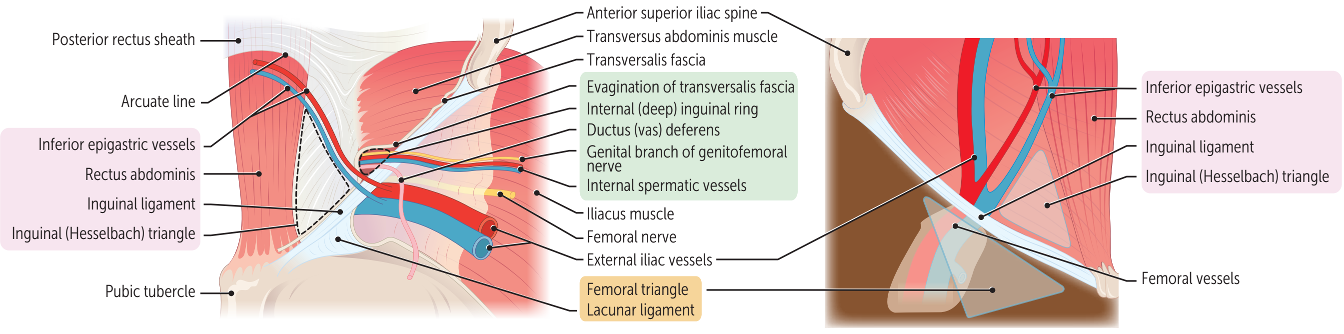
| | | |
|---|---|---|
| ORGANIZATION | **Lateral to medial**: **n**erve-**a**rtery-**v**ein-**l**ymphatics. | You go from **lateral to medial** to find your **navel**. |
| **Femoral triangle** | Contains femoral nerve, artery, vein. | **Venous** near the **penis**. |
| **Femoral sheath** | Fascial tube 3–4 cm below inguinal ligament. Contains femoral vein, artery, and canal (deep inguinal lymph nodes) but not femoral nerve. | |



## Inguinal canal




## Abdominal wall



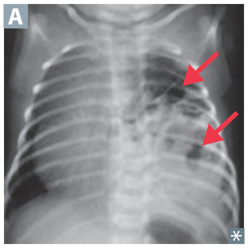

**Anterior abdominal wall**
(viewed from inside)

**Anterior abdominal wall**
(viewed from outside)

**Hernias**

Protrusion of peritoneum through an opening, usually at a site of weakness. Contents may be at risk for incarceration (not reducible back into abdomen/pelvis) and strangulation (ischemia and necrosis). Complicated hernias can present with tenderness, erythema, fever.

**Diaphragmatic hernia**

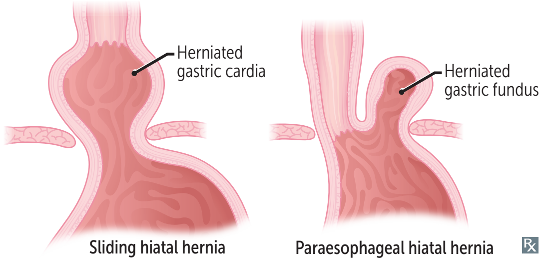



Abdominal structures enter the thorax. Most common causes:

- Infants—congenital defect of pleuroperitoneal membrane → left-sided herniation (right hemidiaphragm is relatively protected by liver) A.
- Adults—laxity/defect of phrenoesophageal membrane → hiatal hernia (herniation of stomach through esophageal hiatus).

Sliding hiatal hernia—gastroesophageal junction is displaced upward as gastric cardia slides into hiatus; "hourglass stomach." Most common type. Associated with GERD.

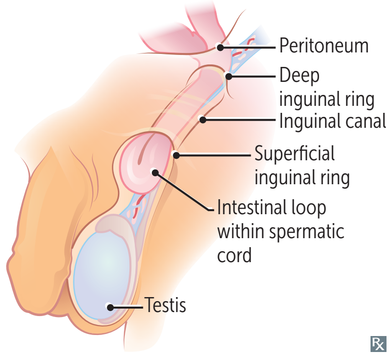
Paraesophageal hiatal hernia—gastroesophageal junction is usually normal but gastric fundus protrudes into the thorax.




**Indirect inguinal hernia**


Goes through the internal (deep) inguinal ring, external (superficial) inguinal ring, and into the groin. Enters internal inguinal ring lateral to inferior epigastric vessels. Caused by failure of processus vaginalis to close (can form hydrocele). May be noticed in **in**fants or discovered in adulthood. Much more common in males B.

Follows the pathway of testicular descent. Covered by all 3 layers of spermatic fascia.



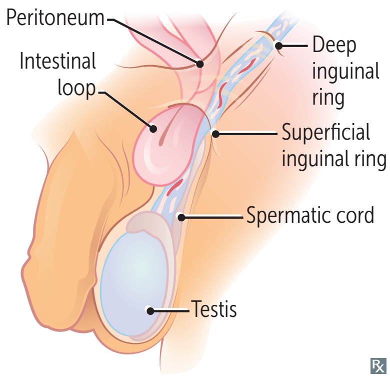

**Direct inguinal hernia**

Protrudes through inguinal (Hesselbach) triangle. Bulges directly through parietal peritoneum medial to the inferior epigastric vessels but lateral to the rectus abdominis. Goes through external (superficial) inguinal ring only. Covered by external spermatic fascia. Usually occurs in older males due to acquired weakness of transversalis fascia.

**MD**s don't **lie**:

**M**edial to inferior epigastric vessels = **D**irect hernia.

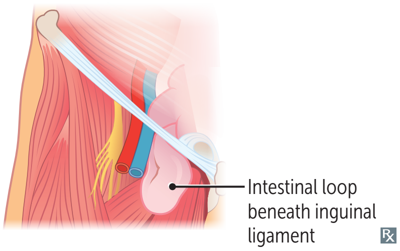
**L**ateral to inferior epigastric vessels = **i**ndirect hernia.




**Femoral hernia**

Protrudes below inguinal ligament through femoral canal below and lateral to pubic tubercle. More common in **fem**ales, but overall inguinal hernias are the most common.

More likely to present with incarceration or strangulation (vs inguinal hernia).



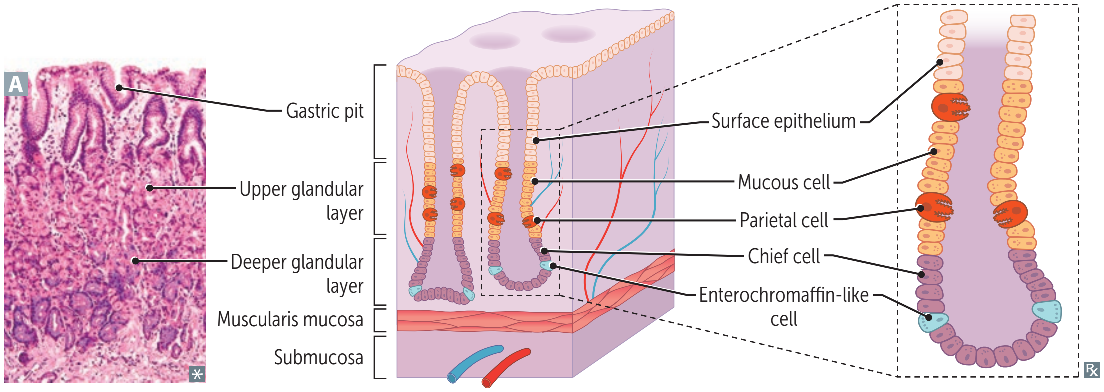
## ▸ GASTROINTESTINAL—PHYSIOLOGY

### Gastrointestinal regulatory substances

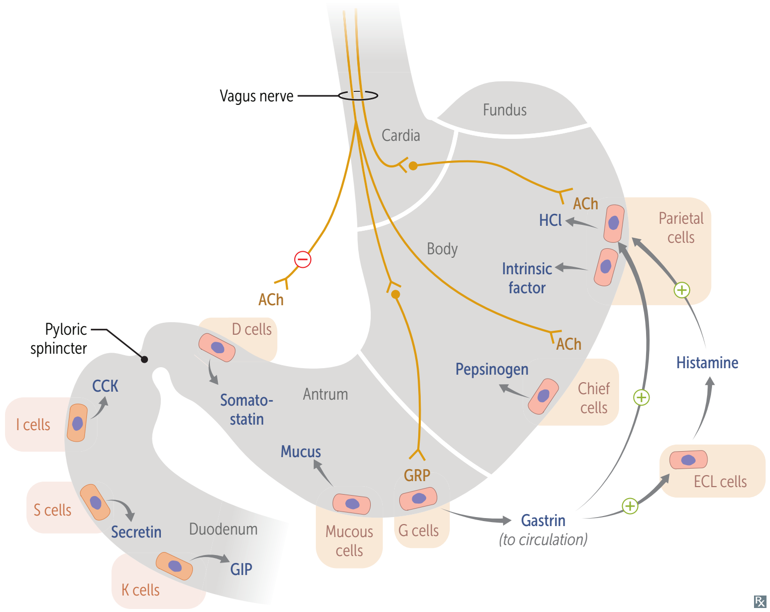
| REGULATORY SUBSTANCE | SOURCE | ACTION | REGULATION | NOTES |
|---|---|---|---|---|
| **Gastrin** | G cells (antrum of stomach, duodenum) | ↑ gastric $H^+$ secretion<br>↑ growth of gastric mucosa<br>↑ gastric motility | ↑ by stomach distention/alkalinization, amino acids, peptides, vagal stimulation via gastrin-releasing peptide (GRP)<br>↓ by pH < 1.5 | ↑ by chronic PPI use<br>↑ in chronic atrophic gastritis (eg, *H pylori*)<br>↑↑ in Zollinger-Ellison syndrome (gastrinoma) |
| **Somatostatin** | D cells (pancreatic islets, GI mucosa) | ↓ gastric acid and pepsinogen secretion<br>↓ pancreatic and small intestine fluid secretion<br>↓ gallbladder contraction<br>↓ insulin and glucagon release | ↑ by acid<br>↓ by vagal stimulation | Inhibits secretion of various hormones (encourages **somato-stas**is)<br>Octreotide is an analog used to treat acromegaly, carcinoid syndrome, VIPoma, and variceal bleeding |
| **Cholecystokinin** | I cells (duodenum, jejunum) | ↑ pancreatic secretion<br>↑ gallbladder contraction<br>↓ gastric emptying<br>↑ sphincter of Oddi relaxation | ↑ by fatty acids, amino acids | Acts on neural muscarinic pathways to cause pancreatic secretion |
| **Secretin** | S cells (duodenum) | ↑ pancreatic $HCO_3^-$ secretion<br>↓ gastric acid secretion<br>↑ bile secretion | ↑ by acid, fatty acids in lumen of duodenum | ↑ $HCO_3^-$ neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function |
| **Glucose-dependent insulinotropic peptide** | K cells (duodenum, jejunum) | Exocrine:<br>↓ gastric $H^+$ secretion<br>Endocrine:<br>↑ insulin release | ↑ by fatty acids, amino acids, oral glucose | Also called gastric inhibitory peptide (GIP)<br>Oral glucose load ↑ insulin compared to IV equivalent due to GIP secretion |
| **Motilin** | Small intestine | Produces migrating motor complexes (MMCs) | ↑ in fasting state | Motilin receptor agonists (eg, erythromycin) are used to stimulate intestinal peristalsis. |
| **Vasoactive intestinal polypeptide** | Parasympathetic ganglia in sphincters, gallbladder, small intestine | ↑ intestinal water and electrolyte secretion<br>↑ relaxation of intestinal smooth muscle and sphincters | ↑ by distention and vagal stimulation<br>↓ by adrenergic input | VIPoma—non-α, non-β islet cell pancreatic tumor that secretes VIP; associated with **W**atery **D**iarrhea, **H**ypokalemia, **A**chlorhydria (**WDHA** syndrome) |
| **Nitric oxide** | | ↑ smooth muscle relaxation, including lower esophageal sphincter (LES) | | Loss of NO secretion is implicated in ↑ LES tone of achalasia |
| **Ghrelin** | Stomach | ↑ appetite ("**ghr**owlin' stomach") | ↑ in fasting state<br>↓ by food | ↑ in Prader-Willi syndrome<br>↓ after gastric bypass surgery |

## Gastrointestinal secretory products

| PRODUCT | SOURCE | ACTION | REGULATION | NOTES |
|---|---|---|---|---|
| **Intrinsic factor** | Parietal cells (stomach A) | Vitamin $B_{12}$–binding protein (required for $B_{12}$ uptake in terminal ileum) | | Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia |
| **Gastric acid** | Parietal cells (stomach) | ↓ stomach pH | ↑ by histamine, vagal stimulation (ACh), gastrin<br>↓ by somatostatin, GIP, prostaglandin, secretin | |
| **Pepsin** | Chief cells (stomach) | Protein digestion | ↑ by vagal stimulation (ACh), local acid | Pepsinogen (inactive) is converted to pepsin (active) in the presence of $H^+$ |
| **Bicarbonate** | Mucosal cells (stomach, duodenum, salivary glands, pancreas) and Brunner glands (duodenum) | Neutralizes acid | ↑ by pancreatic and biliary secretion with secretin | Trapped in mucus that covers the gastric epithelium |



## Locations of gastrointestinal secretory cells



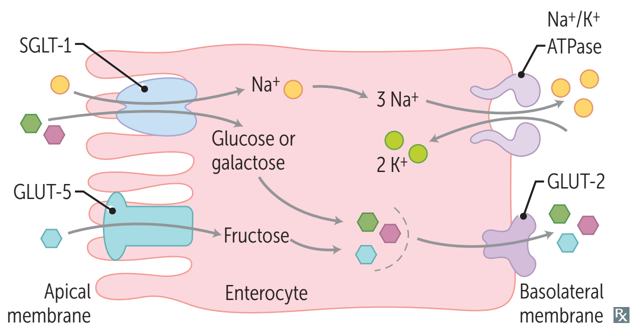

Gastrin ↑ acid secretion primarily through its effects on enterochromaffin-like (ECL) cells (leading to histamine release) rather than through its direct effect on parietal cells.

## Pancreatic secretions

Isotonic fluid; low flow → high $Cl^-$, high flow → high $HCO_3^-$.

| ENZYME | ROLE | NOTES |
|---|---|---|
| **α-amylase** | Starch digestion | Secreted in active form |
| **Lipases** | Fat digestion | |
| **Proteases** | Protein digestion | Includes trypsin, chymotrypsin, elastase, carboxypeptidases<br>Secreted as proenzymes also called zymogens |
| **Trypsinogen** | Converted to active enzyme trypsin → activation of other proenzymes and cleaving of additional trypsinogen molecules into active trypsin (positive feedback loop) | Converted to trypsin by enterokinase/enteropeptidase, a brush-border enzyme on duodenal and jejunal mucosa |

## Carbohydrate absorption



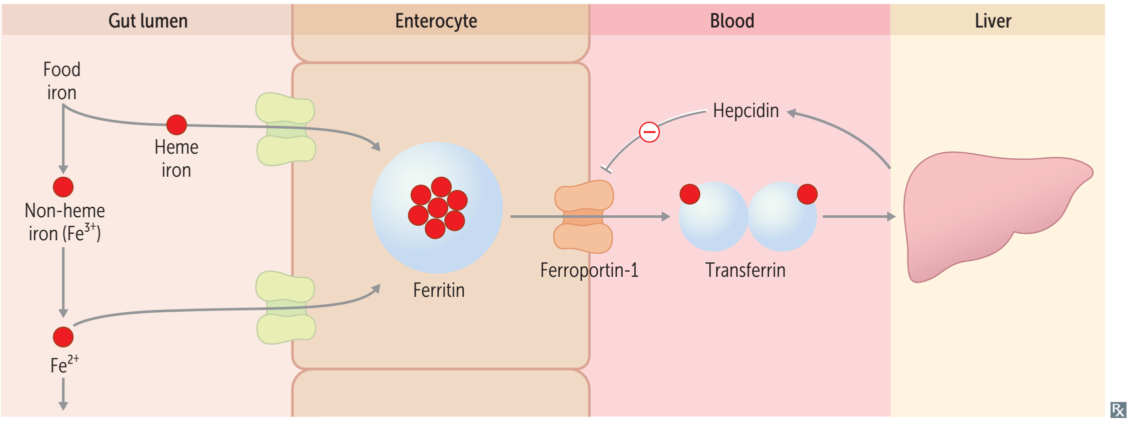

Only monosaccharides (glucose, galactose, fructose) are absorbed by enterocytes. Glucose and galactose are taken up by SGLT1 ($Na^+$ dependent). Fructose is taken up via facilitated diffusion by GLUT5. All are transported to blood by GLUT2.

D-xylose test: simple sugar that is passively absorbed in proximal small intestine; blood and urine levels ↓ with mucosal damage, normal in pancreatic insufficiency.

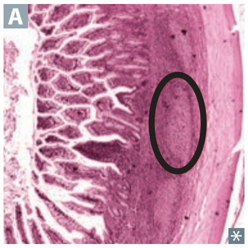
### Vitamin and mineral absorption

Iron absorbed as $Fe^{2+}$ in duodenum.
Folate absorbed in small bowel.
Vitamin $B_{12}$ absorbed in terminal ileum along with bile salts, requires intrinsic factor.

Iron fist, Bro
Vitamin and mineral deficiencies may develop in patients with small bowel disease or after resection (eg, vitamin $B_{12}$ deficiency after terminal ileum resection).




### Peyer patches




Unencapsulated lymphoid tissue A found in lamina propria and submucosa of ileum. Contain specialized M cells that sample and present antigens to iMmune cells.
B cells stimulated in germinal centers of Peyer patches differentiate into IgA-secreting plasma cells, which ultimately reside in lamina propria. IgA receives protective secretory component and is then transported across the epithelium to the gut to deal with intraluminal antigen.

Think of IgA, the Intra-gut Antibody

### Bile

Composed of bile salts (bile acids conjugated to glycine or taurine, making them water soluble), phospholipids, cholesterol, bilirubin, water, and ions. Cholesterol 7α-hydroxylase catalyzes rate-limiting step of bile acid synthesis.
Functions:
- Digestion and absorption of lipids and fat-soluble vitamins
- Bilirubin and cholesterol excretion (body's 1° means of elimination)
- Antimicrobial activity (via membrane disruption)

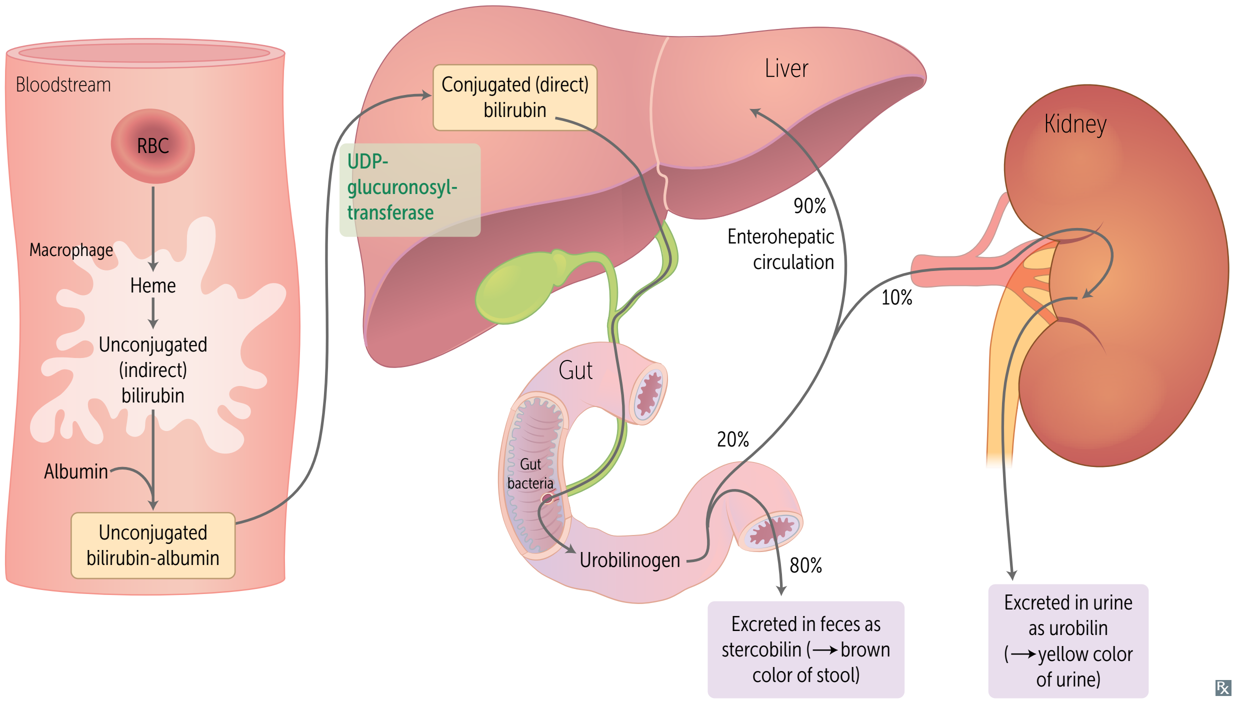
↓ absorption of enteric bile salts at distal ileum (as in short bowel syndrome, Crohn disease) prevents normal fat absorption and may cause bile acid diarrhea.
Calcium, which normally binds oxalate, binds fat instead, so free oxalate is absorbed by gut → ↑ frequency of calcium oxalate kidney stones.

**Bilirubin**

Heme is metabolized by heme oxygenase to biliverdin, which is subsequently reduced to bilirubin. Unconjugated bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile.

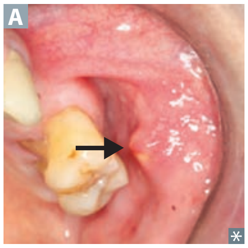
**Di**rect bilirubin: conjugated with glucuronic acid; water soluble (**di**ssolves in water).

**In**direct bilirubin: unconjugated; water **in**soluble.



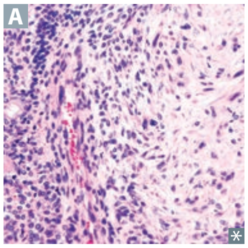
## ▸ GASTROINTESTINAL—PATHOLOGY

### Sialolithiasis




Stone(s) in salivary gland duct A. Can occur in 3 major salivary glands (parotid, submandibular, sublingual). Single stone more common in submandibular gland (Wharton duct).
Associated with salivary stasis (eg, dehydration) and trauma.
Presents as recurrent pre-/periprandial pain and swelling in affected gland.
Sialadenitis—inflammation of salivary gland due to obstruction, infection (eg, *S aureus*, mumps virus), or immune-mediated mechanisms (eg, Sjögren syndrome).

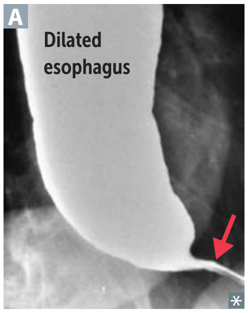
### Salivary gland tumors




Most are benign and commonly affect parotid gland (80-85%). Nearly half of all submandibular gland neoplasms and most sublingual and minor salivary gland tumors are malignant. Typically present as painless mass/swelling. Facial paralysis or pain suggests malignant involvement.

- Pleomorphic adenoma (benign mixed tumor)—most common salivary gland tumor A. Composed of chondromyxoid stroma and epithelium and recurs if incompletely excised or ruptured intraoperatively. May undergo malignant transformation.
- Mucoepidermoid carcinoma—most common malignant tumor, has mucinous and squamous components.
- **War**thin tumor (papillary cystadenoma lymphomatosum)—benign cystic tumor with **germ**inal centers. Associated with tobacco **smoking**. Bilateral in 10%; multifocal in 10%. "**War**riors from **Germ**any love **smoking**."

### Achalasia

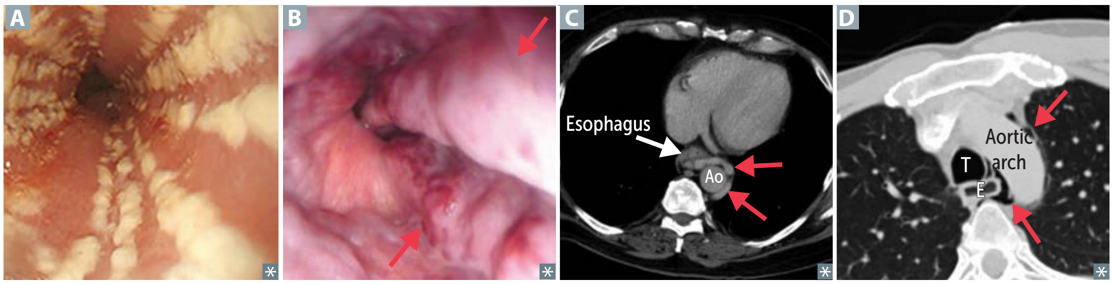



Failure of LES to relax due to degeneration of inhibitory neurons (containing NO and VIP) in the myenteric (Auerbach) plexus of esophageal wall.
1° achalasia is idiopathic. 2° achalasia may arise from Chagas disease (*T cruzi* infection) or extraesophageal malignancies (mass effect or paraneoplastic). **Cha**gas disease can cause a**cha**lasia.
Presents with progressive dysphagia to solids and liquids (vs obstruction—primarily solids).
Associated with ↑ risk of esophageal cancer.

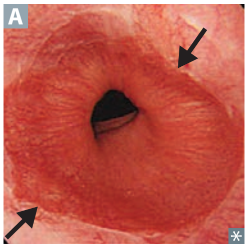
Manometry findings include uncoordinated or absent peristalsis with ↑ LES resting pressure.
Barium swallow shows dilated esophagus with area of distal stenosis ("bird's beak" A).
Treatment: surgery, endoscopic procedures (eg, botulinum toxin injection).

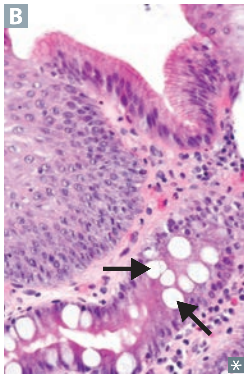
## Esophageal pathologies

| | |
|---|---|
| **Gastroesophageal reflux disease** | Commonly presents as heartburn, regurgitation, dysphagia. May also present as chronic cough, hoarseness (laryngopharyngeal reflux). Associated with asthma. Transient decreases in LES tone. |
| **Eosinophilic esophagitis** | Infiltration of eosinophils in the esophagus often in atopic patients. Etiology is multifactorial. Food allergens → dysphagia, food impaction. Esophageal rings and linear furrows often seen on endoscopy. |
| **Esophagitis** | Associated with reflux, infection in immunocompromised (*Candida*: white pseudomembrane A; HSV-1: punched-out ulcers; CMV: linear ulcers), caustic ingestion, or pill-induced esophagitis (eg, bisphosphonates, tetracycline, NSAIDs, iron, and potassium chloride). |
| **Esophageal strictures** | Associated with caustic ingestion, acid reflux, and esophagitis. |
| **Plummer-Vinson syndrome** | Triad of dysphagia, iron deficiency anemia, esophageal webs. ↑ risk of esophageal squamous cell carcinoma ("Plumber dies"). May be associated with glossitis. |
| **Mallory-Weiss syndrome** | Partial thickness, longitudinal lacerations of gastroesophageal junction, confined to mucosa/submucosa, due to severe vomiting. Often presents with hematemesis +/– abdominal/back pain. Usually found in patients with alcohol use disorder, bulimia nervosa. |
| **Esophageal varices** | Dilated submucosal veins (red arrows in B C) in lower 1/3 of esophagus 2° to portal hypertension. Common in patients with cirrhosis, may be source of life-threatening hematemesis. |
| **Distal esophageal spasm** | Formerly called diffuse esophageal spasm. Spontaneous, nonperistaltic (uncoordinated) contractions of the esophagus with normal LES pressure. Presents with dysphagia and angina-like chest pain. Barium swallow reveals "corkscrew" esophagus. Manometry is diagnostic. Treatment includes nitrates and CCBs. |
| **Scleroderma esophageal involvement** | Esophageal smooth muscle atrophy → ↓ LES pressure and distal esophageal dysmotility → acid reflux and dysphagia → stricture, Barrett esophagus, and aspiration. Part of CREST syndrome. |
| **Esophageal perforation** | Most commonly iatrogenic following esophageal instrumentation. Noniatrogenic causes include spontaneous rupture, foreign body ingestion, trauma, malignancy.<br>May present with pneumomediastinum (arrows in D). Subcutaneous emphysema may be due to dissecting air (signs include crepitus in the neck region or chest wall).<br>Boerhaave syndrome—transmural, usually distal esophageal rupture due to violent retching. |

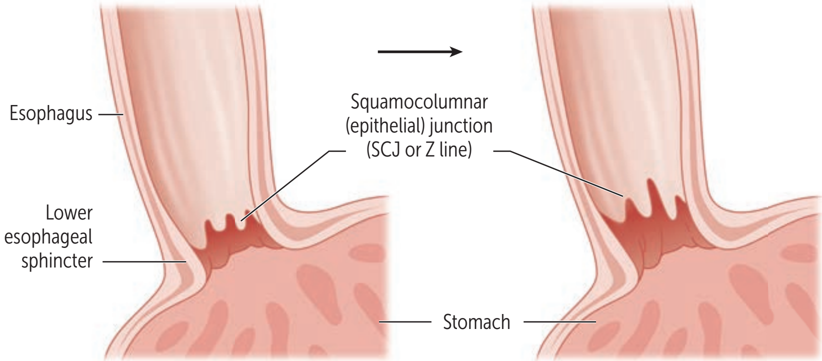


**Barrett esophagus**




Specialized intestinal metaplasia (arrows in A)—replacement of nonkeratinized stratified squamous epithelium with intestinal epithelium (nonciliated columnar with goblet cells [arrows in B]) in distal esophagus. Due to chronic gastroesophageal reflux disease (GERD). Associated with ↑ risk of esophageal adenocarcinoma.




**Esophageal cancer**

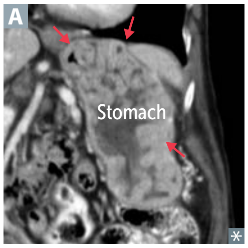
Typically presents with progressive dysphagia (first solids, then liquids) and weight loss. Aggressive course due to lack of serosa in esophageal wall, allowing rapid extension. Poor prognosis due to advanced disease at presentation.

| CANCER | PART OF ESOPHAGUS AFFECTED | RISK FACTORS | PREVALENCE |
|---|---|---|---|
| **Squamous cell carcinoma** | Upper 2/3 | Alcohol, hot liquids, caustic strictures, smoking, achalasia | More common worldwide |
| **Adenocarcinoma** | Lower 1/3 | Chronic GERD, Barrett esophagus, obesity, tobacco smoking | More common in America |

## Gastritis

| | | |
|---|---|---|
| **Acute gastritis** | Erosions can be caused by:<br>▪ NSAIDs—↓ $PGE_2$ → ↓ gastric mucosa protection<br>▪ **Burns** (**Curling** ulcer)—hypovolemia → mucosal ischemia<br>▪ **Brain** injury (**Cush**ing ulcer)—↑ vagal stimulation → ↑ ACh → ↑ $H^+$ production | Especially common among patients with alcohol use disorder and those taking daily NSAIDs (eg, for rheumatoid arthritis)<br>**Burn**ed by the **Curling** iron<br>Always **Cush**ion the **brain** |
| **Chronic gastritis** | Mucosal inflammation, often leading to atrophy (hypochlorhydria → hypergastrinemia) and intestinal metaplasia (↑ risk of gastric cancers) | |
| *H pylori* | Most common. ↑ risk of peptic ulcer disease, MALT lymphoma | Affects antrum first and spreads to body of stomach |
| Autoimmune | Autoantibodies to the $H^+/K^+$ ATPase on parietal cells and to intrinsic factor. ↑ risk of pernicious anemia | Affects body/fundus of stomach |

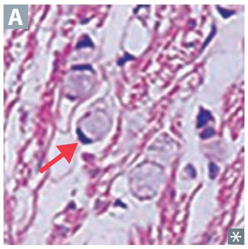
## Ménétrier disease




Hyperplasia of gastric mucosa → hypertrophied rugae ("**wavy**" like brain gyri A). Causes excess mucus production with resultant protein loss and parietal cell atrophy with ↓ acid production. Precancerous.

Presents with **W**eight loss, **A**norexia, **V**omiting, **E**pigastric pain, **E**dema (due to protein loss; pronounce "**WAVEE**").

## Gastric cancer




Most commonly gastric adenocarcinoma; lymphoma, GI stromal tumor, carcinoid (rare). Early aggressive local spread with node/liver metastases. Often presents late, with weight loss, abdominal pain, early satiety, and in some cases acanthosis nigricans or Leser-Trélat sign.

- Intestinal—associated with *H pylori*, dietary nitrosamines (smoked foods), tobacco smoking, achlorhydria, chronic gastritis. Commonly on lesser curvature; looks like ulcer with raised margins.
- Diffuse—not associated with *H pylori*; most cases due to E-cadherin mutation; signet ring cells (mucin-filled cells with peripheral nuclei) A; stomach wall grossly thickened and leathery (linitis plastica).

**Virchow node**—involvement of left supraclavicular node by metastasis from stomach.

**Krukenberg tumor**—metastasis to ovaries (typically bilateral). Abundant mucin-secreting, signet ring cells.

**Sister Mary Joseph nodule**—subcutaneous periumbilical metastasis.

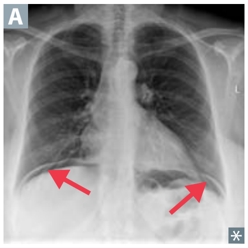
**Blumer shelf**—palpable mass on digital rectal exam suggesting metastasis to rectouterine pouch (pouch of Douglas).

## Peptic ulcer disease

| | Gastric ulcer | Duodenal ulcer |
|---|---|---|
| PAIN | Can be greater with meals—weight loss | Decreases with meals—weight gain |
| *H PYLORI* INFECTION | ~ 70% | ~ 90% |
| MECHANISM | ↓ mucosal protection against gastric acid | ↓ mucosal protection or ↑ gastric acid secretion |
| OTHER CAUSES | NSAIDs | Zollinger-Ellison syndrome |
| RISK OF CARCINOMA | ↑ | Generally benign |
| OTHER | Biopsy margins to rule out malignancy | Benign-appearing ulcers are not routinely biopsied |

## Ulcer complications

| | |
|---|---|
| **Hemorrhage** | Gastric, duodenal (posterior > anterior). Most common complication.<br>Ruptured gastric ulcer on the lesser curvature of stomach → bleeding from left gastric artery.<br>An ulcer on the posterior wall of duodenum → bleeding from gastroduodenal artery. |
| **Obstruction** | Pyloric channel, duodenal. |
| **Perforation** | Duodenal (anterior > posterior).<br>Anterior duodenal ulcers can perforate into the anterior abdominal cavity, potentially leading to pneumoperitoneum.<br>May see free air under diaphragm (pneumoperitoneum) A with referred pain to the shoulder via irritation of phrenic nerve. |




## Acute gastrointestinal bleeding

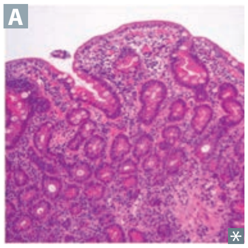
Upper GI bleeding—originates **proximal** to ligament of Treitz (suspensory ligament of duodenum). Usually presents with hematemesis and/or melena. Associated with peptic ulcer disease, variceal hemorrhage.

Lower GI bleeding—originates **distal** to ligament of Treitz. Usually presents with hematochezia. Associated with IBD, diverticulosis, angiodysplasia, hemorrhoids, cancer.

**Malabsorption syndromes**

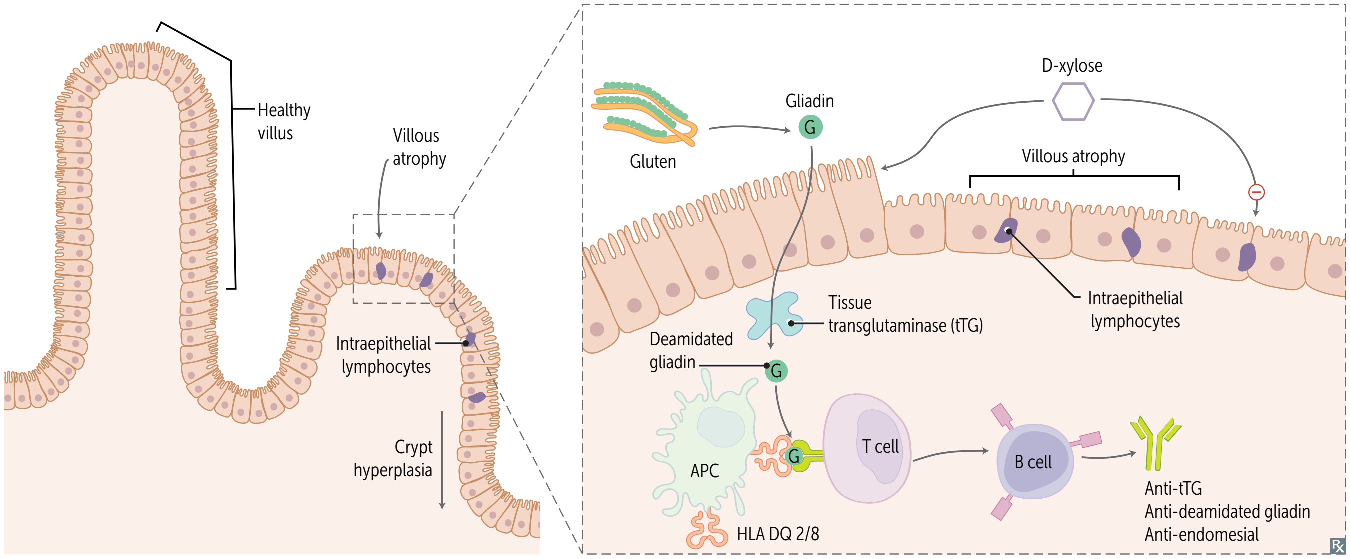
Can cause diarrhea, steatorrhea, weight loss, weakness, vitamin and mineral deficiencies. Screen for fecal fat (eg, Sudan stain).

**Celiac disease**




Also called gluten-sensitive enteropathy, celiac sprue. Autoimmune-mediated intolerance of gliadin (gluten protein found in wheat, barley, rye). Associated with HLA-DQ2, HLA-DQ8, northern European descent.
Primarily affects distal duodenum and/or proximal jejunum → malabsorption and steatorrhea.
Treatment: gluten-free diet.

Associated with dermatitis herpetiformis, ↓ bone density, moderately ↑ risk of malignancy (eg, T-cell lymphoma).
D-xylose test: abnormal.
Serology: ⊕ IgA anti-tissue transglutaminase (IgA tTG), anti-endomysial, and anti-deamidated gliadin peptide antibodies.
Histology: villous atrophy, crypt hyperplasia A, intraepithelial lymphocytosis.




**Lactose intolerance**

Lactase deficiency. Normal-appearing villi, except when 2° to injury at tips of villi (eg, viral enteritis). Osmotic diarrhea with ↓ stool pH (colonic bacteria ferment lactose).

Lactose hydrogen breath test: ⊕ for lactose malabsorption if post-lactose breath hydrogen value rises > 20 ppm compared with baseline.

**Pancreatic insufficiency**

Due to chronic pancreatitis, cystic fibrosis, obstructing cancer. Causes malabsorption of fat and fat-soluble vitamins (A, D, E, K) as well as vitamin $B_{12}$.

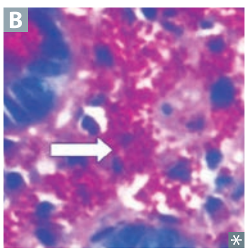
↓ duodenal bicarbonate (and pH) and fecal elastase.
D-xylose test: normal.

**Tropical sprue**

Similar findings as celiac sprue (affects small bowel), but responds to antibiotics. Cause is unknown, but seen in residents of or recent visitors to tropics.

↓ mucosal absorption affecting duodenum and jejunum but can involve ileum with time. Associated with megaloblastic anemia due to folate deficiency and, later, $B_{12}$ deficiency.

**Whipple disease**

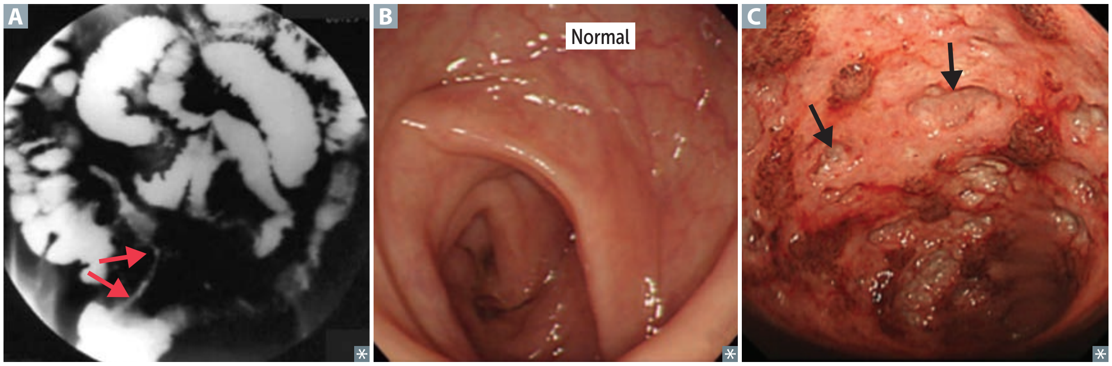



Infection with *Tropheryma whipplei* (intracellular gram ⊕); PAS ⊕ foamy macrophages in intestinal lamina propria B, mesenteric nodes. Cardiac symptoms, Arthralgias, and Neurologic symptoms are common. Diarrhea/steatorrhea occur later in disease course. Most common in older males.

PASs the foamy Whipped cream in a CAN.

## Inflammatory bowel diseases

| | Crohn disease | Ulcerative colitis |
|---|---|---|
| LOCATION | Any portion of the GI tract, usually the terminal ileum and colon. Skip lesions, rectal sparing. | Colitis = colon inflammation. Continuous colonic lesions, always with rectal involvement. |
| GROSS MORPHOLOGY | Transmural inflammation → fistulas. Cobblestone mucosa, creeping fat, bowel wall thickening ("string sign" on small bowel follow-through A), linear ulcers, fissures. | Mucosal and submucosal inflammation only. Friable mucosa with superficial and/or deep ulcerations (compare normal B with diseased C). Loss of haustra → "lead pipe" appearance on imaging. |
| MICROSCOPIC MORPHOLOGY | Noncaseating granulomas and lymphoid aggregates. Th1 mediated. | Crypt abscesses and ulcers, bleeding, no granulomas. Th2 mediated. |
| COMPLICATIONS | Malabsorption/malnutrition, colorectal cancer (↑ risk with pancolitis). | |
| | Fistulas (eg, enterovesical fistulae, which can cause recurrent UTI and pneumaturia), phlegmon/abscess, strictures (causing obstruction), perianal disease. | Fulminant colitis, toxic megacolon, perforation. |
| INTESTINAL MANIFESTATION | Diarrhea that may or may not be bloody. | Bloody diarrhea. |
| EXTRAINTESTINAL MANIFESTATIONS | Rash (pyoderma gangrenosum, erythema nodosum), eye inflammation (episcleritis, uveitis), oral ulcerations (aphthous stomatitis), arthritis (peripheral, spondylitis). | |
| | Kidney stones (usually calcium oxalate), gallstones. May be ⊕ for anti-*Saccharomyces cerevisiae* antibodies (ASCA). | 1° sclerosing cholangitis. Associated with MPO-ANCA/p-ANCA. |
| TREATMENT | Corticosteroids, azathioprine, antibiotics (eg, ciprofloxacin, metronidazole), biologics (eg, infliximab, adalimumab). | 5-aminosalicylic acid preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy. |




**Microscopic colitis** Inflammatory disease of colon that causes chronic watery diarrhea. Most common in older females. Colonic mucosa appears normal on endoscopy. Histology shows inflammatory infiltrate in lamina propria with thickened subepithelial collagen band or intraepithelial lymphocytes.

### Irritable bowel syndrome

Recurrent abdominal pain associated with ≥ 2 of the following:
- Related to defecation
- Change in stool frequency
- Change in form (consistency) of stool

No structural abnormalities. Most common in middle-aged females. Chronic symptoms may be diarrhea-predominant, constipation-predominant, or mixed. Pathophysiology is multifaceted.

First-line treatment is lifestyle modification and dietary changes.

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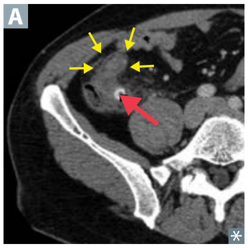
### Appendicitis




Acute inflammation of the appendix (yellow arrows in A), can be due to obstruction by fecalith (red arrow in A) (in adults) or lymphoid hyperplasia (in children).

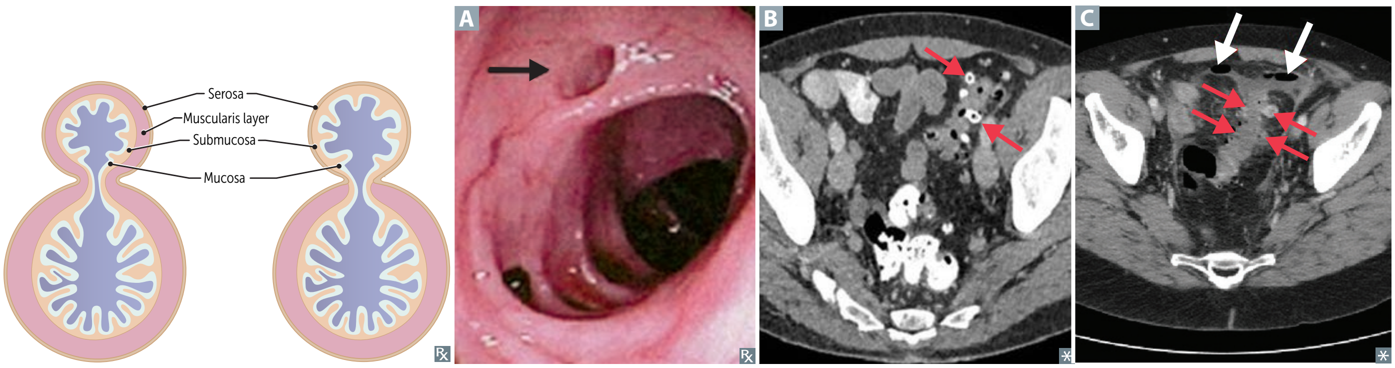
Proximal obstruction of appendiceal lumen produces closed-loop obstruction → ↑ intraluminal pressure → stimulation of visceral afferent nerve fibers at T8-T10 → initial diffuse periumbilical pain → inflammation extends to serosa and irritates parietal peritoneum. Pain localized to RLQ/McBurney point (1/3 the distance from right anterior superior iliac spine to umbilicus). Nausea, fever; may perforate → peritonitis; may elicit psoas, obturator, and Rovsing signs, guarding and rebound tenderness on exam.

Treatment: appendectomy.

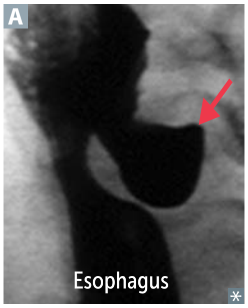
---

### Diverticula of the GI tract

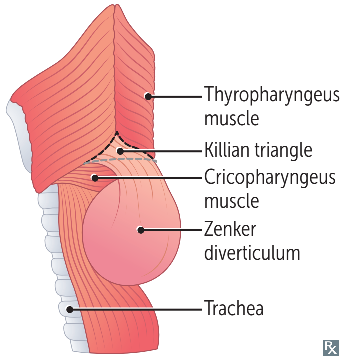
| | | |
|---|---|---|
| **Diverticulum** | Blind pouch A protruding from the alimentary tract that communicates with the lumen of the gut. Most diverticula (esophagus, stomach, duodenum, colon) are acquired and are termed "false diverticula." | "True" diverticulum—all gut wall layers outpouch (eg, Meckel).<br>"False" diverticulum or pseudodiverticulum—only mucosa and submucosa outpouch. Occur especially where vasa recta perforate muscularis externa. |
| **Diverticulosis** | Many false diverticula of the colon B, commonly sigmoid. Common (in ~ 50% of people > 60 years). Caused by ↑ intraluminal pressure and focal weakness in colonic wall. Associated with obesity and diets low in fiber, high in total fat/red meat. | Often asymptomatic or associated with vague discomfort.<br>Complications include diverticular bleeding (painless hematochezia), diverticulitis. |
| **Diverticulitis** | Inflammation of diverticula with wall thickening (red arrows in C) classically causing LLQ pain, fever, leukocytosis. Treat with antibiotics. | Complications: abscess, fistula (colovesical fistula → pneumaturia), obstruction (inflammatory stenosis), perforation (white arrows in C) (→ peritonitis). Hematochezia is rare. |



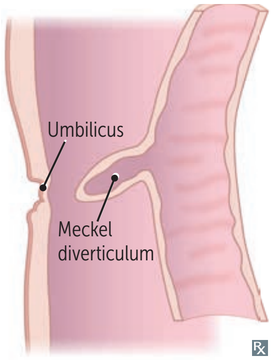
### Zenker diverticulum




Pharyngoesophageal **false** diverticulum A. Esophageal dysmotility causes herniation of mucosal tissue at Killian triangle between the thyropharyngeal and cricopharyngeal parts of the inferior pharyngeal constrictor. Presenting symptoms: dysphagia, obstruction, gurgling, aspiration, foul breath, neck mass. Most common in elderly males.




### Meckel diverticulum

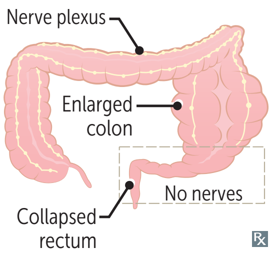



**True** diverticulum. Persistence of the vitelline (omphalomesenteric) duct. May contain ectopic acid–secreting gastric mucosa and/or pancreatic tissue. Most common congenital anomaly of GI tract. Can cause hematochezia/melena (less common), RLQ pain, intussusception, volvulus, or obstruction near terminal ileum.

Diagnosis: $^{99m}$Tc-pertechnetate scan (aka Meckel scan) for uptake by heterotopic gastric mucosa.

The rule of 2's:
- 2 times as likely in males.
- 2 inches long.
- 2 feet from the ileocecal valve.
- 2% of population.
- Commonly presents in first 2 years of life.
- May have 2 types of epithelia (gastric/pancreatic).

### Hirschsprung disease




Congenital megacolon characterized by lack of ganglion cells/enteric nervous plexuses (Auerbach and Meissner plexuses) in distal segment of colon. Due to failure of neural crest cell migration. Associated with loss of function mutations in *RET*.

Presents with bilious emesis, abdominal distention, and failure to pass meconium within 48 hours → chronic constipation. Normal portion of the colon proximal to the aganglionic segment is dilated, resulting in a "transition zone."

Risk ↑ with Down syndrome.

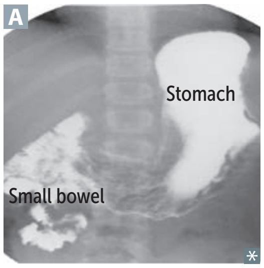
Explosive expulsion of feces (squirt sign) → empty rectum on digital exam.

Diagnosed by absence of ganglion cells on rectal suction biopsy.

Treatment: resection.

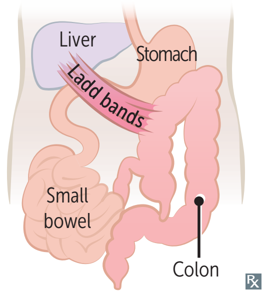
*RET* mutation in the REcTum.

## Malrotation

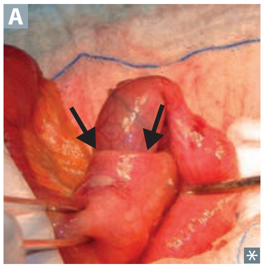


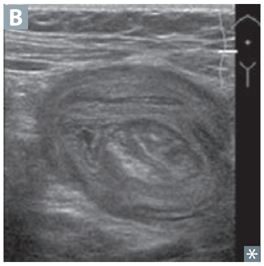

Anomaly of midgut rotation during fetal development → improper positioning of bowel (small bowel clumped on the right side) A, formation of fibrous bands (Ladd bands).

Can lead to volvulus, duodenal obstruction.




## Intussusception




Telescoping A of proximal bowel segment into a distal segment, commonly at the ileocecal junction. Most commonly idiopathic, but may be due to lead point.

Compromised blood supply → intermittent, severe, abdominal pain often with "currant jelly" dark red stools.

Majority of cases in infants, unusual in adults.

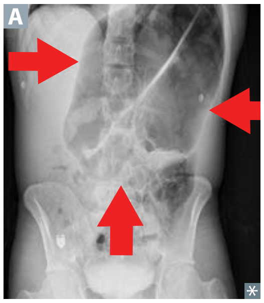
Most common pathologic lead point:
- Children—Meckel diverticulum
- Adults—intraluminal mass/tumor

Physical exam—sausage-shaped mass in right abdomen, patient may draw legs to chest to ease pain.

Imaging—Ultrasound/CT may show "target sign" B.

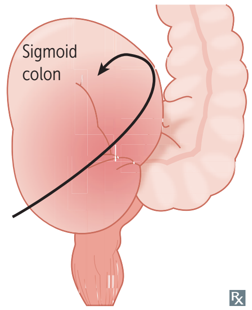
May be associated with IgA vasculitis (HSP), recent viral infection (eg, adenovirus; Peyer patch hypertrophy creates lead point).

### Volvulus



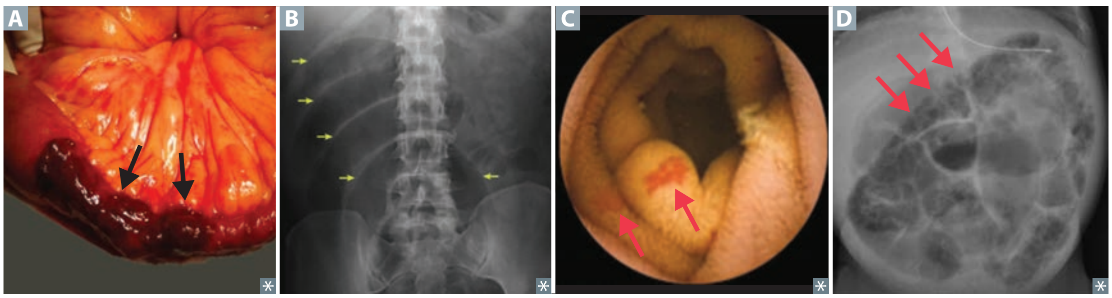

Twisting of portion of bowel around its mesentery; can lead to obstruction and infarction. Can occur throughout the GI tract.

- **M**idgut volvulus more common in infants and children (**m**inors)
- **S**igmoid volvulus (coffee bean sign on x-ray A) more common in **s**eniors (elderly)

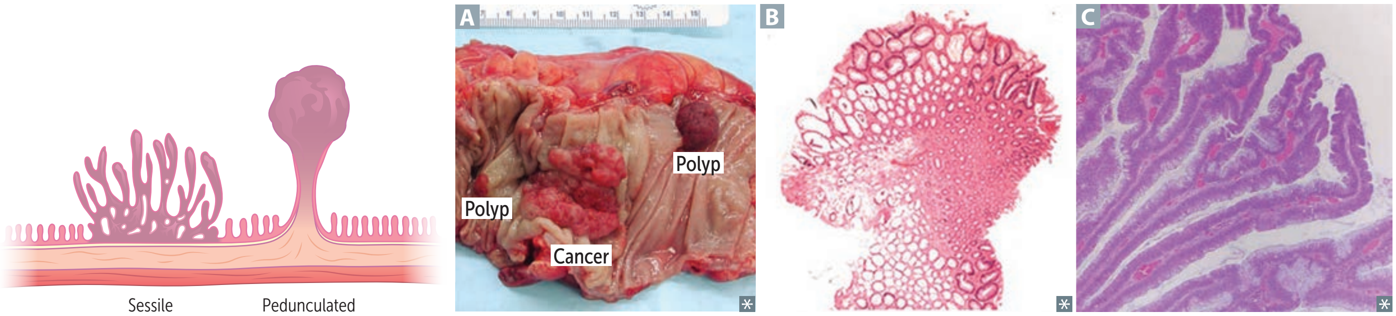



### Other intestinal disorders

| | |
|---|---|
| **Acute mesenteric ischemia** | Critical blockage of intestinal blood flow (often embolic occlusion of SMA) → small bowel necrosis A → abdominal pain out of proportion to physical findings. May see red "currant jelly" stools. |
| **Adhesion** | Fibrous band of scar tissue; commonly forms after surgery. Most common cause of small bowel obstruction, demonstrated by multiple dilated small bowel loops on x-ray (arrows in B). |
| **Angiodysplasia** | Tortuous dilation of vessels C → hematochezia. Most often found in the right-sided colon. More common in older patients. Confirmed by angiography. Associated with end-stage renal disease, von Willebrand disease, aortic stenosis. |
| **Chronic mesenteric ischemia** | "Intestinal angina": atherosclerosis of celiac artery, SMA, or IMA → intestinal hypoperfusion → postprandial epigastric pain → food aversion and weight loss. |
| **Colonic ischemia** | Crampy abdominal pain followed by hematochezia. Commonly occurs at watershed areas (splenic flexure, rectosigmoid junction). Typically affects elderly. Thumbprint sign on imaging due to mucosal edema/hemorrhage. |
| **Ileus** | Intestinal hypomotility without obstruction → constipation and ↓ flatus; distended/tympanic abdomen with ↓ bowel sounds. Associated with abdominal surgeries, opiates, hypokalemia, sepsis. No transition zone on imaging. Treatment: bowel rest, electrolyte correction, cholinergic drugs (stimulate intestinal motility). |
| **Meconium ileus** | Meconium plug obstructs intestine, prevents stool passage at birth. Associated with cystic fibrosis. |
| **Necrotizing enterocolitis** | Seen in premature, formula-fed infants with immature immune system. Necrosis of intestinal mucosa (most commonly terminal ileum and proximal colon), which can lead to pneumatosis intestinalis (arrows in D), pneumoperitoneum, portal venous gas. |



| | |
|---|---|
| **Colonic polyps** | Growths of tissue within the colon A. Grossly characterized as flat, sessile, or pedunculated on the basis of protrusion into colonic lumen. Generally classified by histologic type. |
| HISTOLOGIC TYPE | CHARACTERISTICS |
| Generally nonneoplastic | |
| **Hamartomatous polyps** | Solitary lesions do not have significant risk of transformation. Growths of normal colonic tissue with distorted architecture. Associated with Peutz-Jeghers syndrome and juvenile polyposis. |
| **Hyperplastic polyps** | Most common; generally smaller and predominantly located in rectosigmoid region. Occasionally evolves into serrated polyps and more advanced lesions. |
| **Inflammatory pseudopolyps** | Due to mucosal erosion in inflammatory bowel disease. |
| **Mucosal polyps** | Small, usually < 5 mm. Look similar to normal mucosa. Clinically insignificant. |
| **Submucosal polyps** | May include lipomas, leiomyomas, fibromas, and other lesions. |
| Potentially malignant | |
| **Adenomatous polyps** | Neoplastic, via chromosomal instability pathway with mutations in *APC* and *KRAS*. Tubular B histology has less malignant potential than villous C ("**villous** histology is **vill**ain**ous**"); tubulovillous has intermediate malignant potential. Usually asymptomatic; may present with occult bleeding. |
| **Serrated polyps** | Neoplastic. Characterized by CpG island methylator phenotype (CIMP; cytosine base followed by guanine, linked by a phosphodiester bond). Defect may silence *MMR* gene (DNA mismatch repair) expression. Mutations lead to microsatellite instability and mutations in *BRAF*. "Saw-tooth" pattern of crypts on biopsy. Up to 20% of cases of sporadic CRC. |




## Polyposis syndromes

| | |
|---|---|
| **Familial adenomatous polyposis** | Autosomal dominant mutation of *APC* tumor suppressor gene on chromosome 5q21-q22. 2-hit hypothesis. Thousands of polyps arise starting after puberty; pancolonic; always involves rectum. Prophylactic colectomy or else 100% progress to CRC. |
| **Gardner syndrome** | FAP + osseous and soft tissue tumors (eg, osteomas of skull or mandible), congenital hypertrophy of retinal pigment epithelium, impacted/supernumerary teeth. |
| **Turcot syndrome** | FAP or Lynch syndrome + malignant CNS tumor (eg, medulloblastoma, glioma). **Tur**cot = **Tur**ban. |
| **Peutz-Jeghers syndrome** | Autosomal dominant syndrome featuring numerous hamartomas throughout GI tract, along with hyperpigmented macules on mouth, lips, hands, genitalia. Associated with ↑ risk of breast and GI cancers (eg, colorectal, stomach, small bowel, pancreatic). |
| **Juvenile polyposis syndrome** | Autosomal dominant syndrome in children (typically < 5 years old) featuring numerous hamartomatous polyps in the colon, stomach, small bowel. Associated with ↑ risk of CRC. |

**Lynch syndrome**

Previously called hereditary nonpolyposis colorectal cancer (HNPCC). Autosomal dominant mutation of mismatch repair genes (eg, *MLH1*, *MSH2*) with subsequent microsatellite instability. ~ 80% progress to CRC. Proximal colon is always involved. Associated with endometrial, ovarian, and skin cancers.

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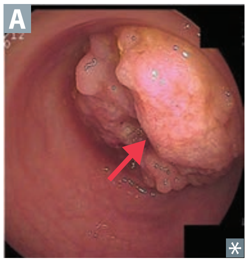
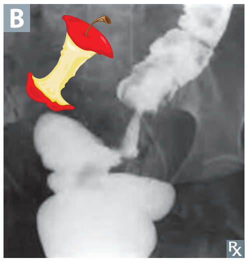
## Colorectal cancer

**DIAGNOSIS**





Iron deficiency anemia in males (especially > 50 years old) and postmenopausal females raises suspicion.

Screening:
- Average risk: screen at age 50 with colonoscopy (polyp seen in A); alternatives include flexible sigmoidoscopy, fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), FIT-fecal DNA, CT colonography.
- Patients with a first-degree relative who has colon cancer: screen at age 40 with colonoscopy, or 10 years prior to the relative's presentation.
- Patients with IBD are screened more regularly.

"Apple core" lesion seen on barium enema x-ray B.

CEA tumor marker: good for monitoring recurrence, should not be used for screening.

**EPIDEMIOLOGY**

Most patients are > 50 years old. ~ 25% have a family history.

**PRESENTATION**

Rectosigmoid > ascending > descending.

Most are asymptomatic. Right side (cecal, ascending) associated with occult bleeding; left side (rectosigmoid) associated with hematochezia and obstruction (narrower lumen → ↓ stool caliber).

Ascending—exophytic mass, iron deficiency anemia, weight loss.

Descending—infiltrating mass, partial obstruction, colicky pain, hematochezia.

Can present with *S bovis* (*gallolyticus*) bacteremia/endocarditis or as an episode of diverticulitis.

**RISK FACTORS**

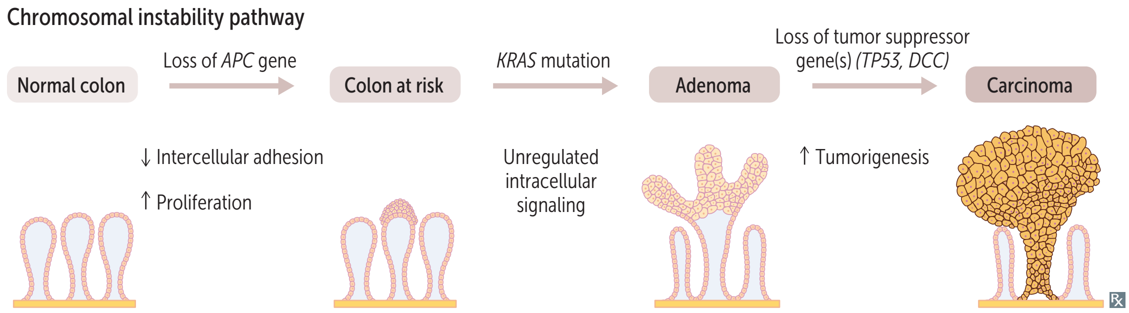
Adenomatous and serrated polyps, familial cancer syndromes, IBD, tobacco use, diet of processed meat with low fiber.

### Molecular pathogenesis of colorectal cancer

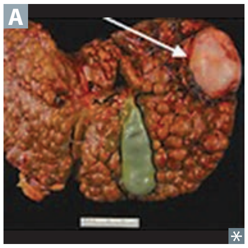
Chromosomal instability pathway: mutations in *APC* cause FAP and most sporadic cases of CRC via adenoma-carcinoma sequence.

Microsatellite instability pathway: mutations or methylation of mismatch repair genes (eg, *MLH1*) cause Lynch syndrome and some sporadic CRC via serrated polyp pathway. Usually leads to right-sided CRC.

Overexpression of COX-2 has been linked to colorectal cancer, NSAIDs may be chemopreventive.

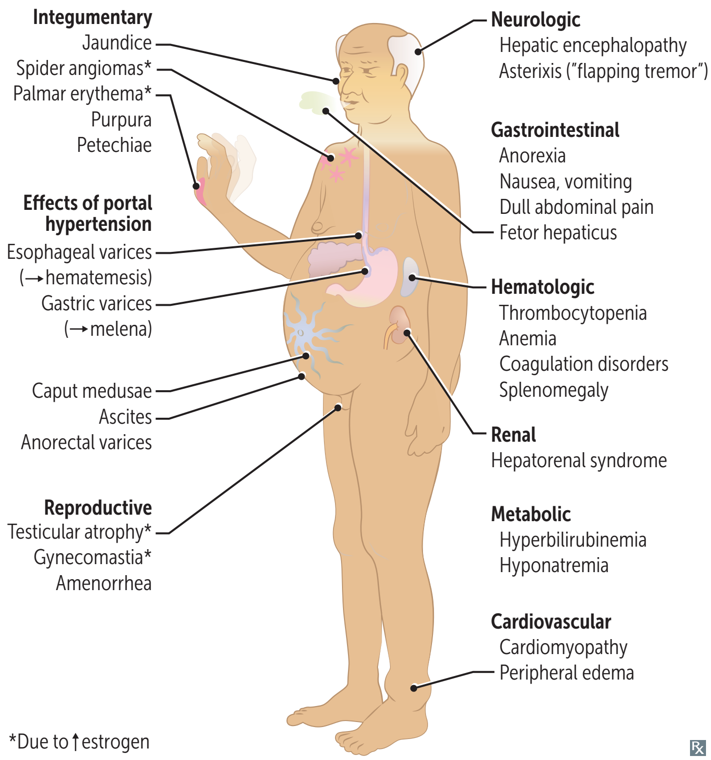



### Cirrhosis and portal hypertension




**Cirrhosis**—diffuse bridging fibrosis (via stellate cells) and regenerative nodules (arrows show splenomegaly) disrupt normal architecture of liver; ↑ risk for hepatocellular carcinoma (white arrow in A). Etiologies include alcohol, nonalcoholic steatohepatitis, chronic viral hepatitis, autoimmune hepatitis, biliary disease, genetic/metabolic disorders.

**Portal hypertension**—↑ pressure in portal venous system. Etiologies include cirrhosis (most common cause in developed countries), vascular obstruction (eg, portal vein thrombosis, Budd-Chiari syndrome), schistosomiasis.



| | |
|---|---|
| **Spontaneous bacterial peritonitis** | Also called 1° bacterial peritonitis. Common and potentially fatal bacterial infection in patients with cirrhosis and ascites. Often asymptomatic, but can cause fevers, chills, abdominal pain, ileus, or worsening encephalopathy. Commonly caused by gram ⊖ organisms (eg, *E coli*, *Klebsiella*) or less commonly gram ⊕ *Streptococcus*.<br>Diagnosis: paracentesis with ascitic fluid absolute neutrophil count (ANC) > 250 cells/mm$^3$. Empiric first-line treatment is 3rd generation cephalosporin (eg, cefotaxime). |

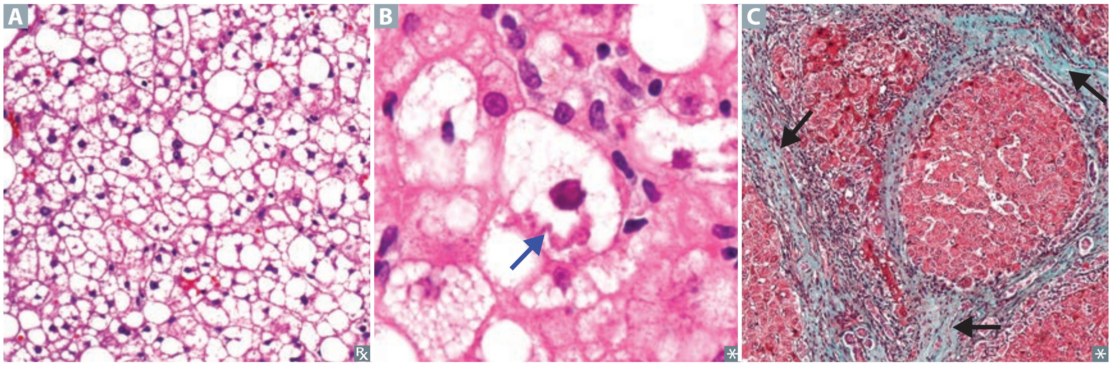
## Serum markers of liver pathology

| | |
|---|---|
| ENZYMES RELEASED IN LIVER DAMAGE | |
| **Aspartate aminotransferase and alanine aminotransferase** | ↑ in most liver disease: ALT > AST<br>↑ in **alcoholic** liver disease: **AST** > ALT (ratio usually > 2:1, AST does not typically exceed 500 U/L in alcoholic hepatitis). Make a to**AST** with **alcohol**<br>AST > ALT in nonalcoholic liver disease suggests progression to advanced fibrosis or cirrhosis<br>↑↑↑ aminotransferases (>1000 U/L): differential includes drug-induced liver injury (eg, acetaminophen toxicity), ischemic hepatitis, acute viral hepatitis, autoimmune hepatitis |
| **Alkaline phosphatase** | ↑ in cholestasis (eg, biliary obstruction), infiltrative disorders, bone disease |
| **γ-glutamyl transpeptidase** | ↑ in various liver and biliary diseases (just as ALP can), but not in bone disease; associated with alcohol use |
| FUNCTIONAL LIVER MARKERS | |
| **Bilirubin** | ↑ in various liver diseases (eg, biliary obstruction, alcoholic or viral hepatitis, cirrhosis), hemolysis |
| **Albumin** | ↓ in advanced liver disease (marker of liver's biosynthetic function) |
| **Prothrombin time** | ↑ in advanced liver disease (↓ production of clotting factors, thereby measuring the liver's biosynthetic function) |
| **Platelets** | ↓ in advanced liver disease (↓ thrombopoietin, liver sequestration) and portal hypertension (splenomegaly/splenic sequestration) |

| | | |
|---|---|---|
| **Reye syndrome** | Rare, often fatal childhood hepatic encephalopathy.<br>Associated with viral infection (especially VZV and influenza) that has been treated with aspirin. Aspirin metabolites ↓ β-oxidation by reversible inhibition of mitochondrial enzymes.<br>Findings: mitochondrial abnormalities, fatty liver (microvesicular fatty changes), hypoglycemia, vomiting, hepatomegaly, coma. | Avoid aspirin (**ASA**) in children, except in Kaw**ASA**ki disease.<br>Salicylates aren't a ray (**Reye**) of sun**SHINE** for kids:<br>**S**teatosis of liver/hepatocytes<br>**H**ypoglycemia/**H**epatomegaly<br>**I**nfection (VZV, influenza)<br>**N**ot awake (coma)<br>**E**ncephalopathy |

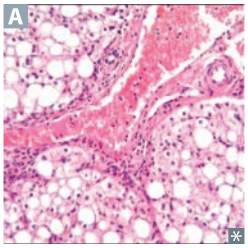
## Alcoholic liver disease

| | |
|---|---|
| **Hepatic steatosis** | Macrovesicular fatty change A that may be reversible with alcohol cessation. |
| **Alcoholic hepatitis** | Requires sustained, long-term consumption. Swollen and necrotic hepatocytes with neutrophilic infiltration. Mallory bodies B (intracytoplasmic eosinophilic inclusions of damaged keratin filaments). |
| **Alcoholic cirrhosis** | Final and usually irreversible form. Sclerosis around central vein (arrows in C) may be seen in early disease. Regenerative nodules surrounded by fibrous bands in response to chronic liver injury → portal hypertension and end-stage liver disease. |




**Nonalcoholic fatty liver disease**

Metabolic syndrome (insulin resistance); obesity → fatty infiltration of hepatocytes A → cellular "ballooning" and eventual necrosis. May cause cirrhosis and HCC. Independent of alcohol use.




**Autoimmune hepatitis**

Chronic inflammatory liver disease. More common in females. May be asymptomatic or present with fatigue, nausea, pruritus. May be associated with ⊕ antinuclear, anti-smooth muscle and anti-liver/kidney microsomal-1 antibodies. Labs: ↑ ALT and AST. Histology: portal and periportal lymphoplasmacytic infiltrate.

**Hepatic encephalopathy**

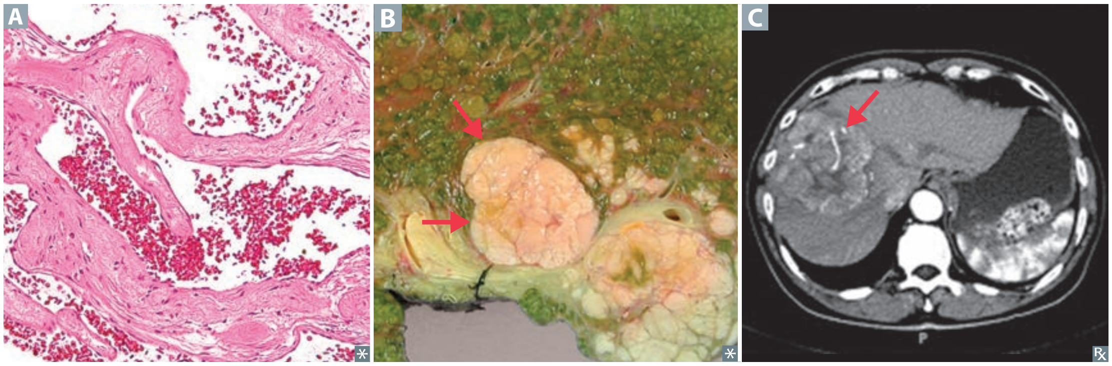
Cirrhosis → portosystemic shunts → ↓ $NH_3$ metabolism → neuropsychiatric dysfunction. Reversible neuropsychiatric dysfunction ranging from disorientation/asterixis (mild) to difficult arousal or coma (severe).

Triggers:
- ↑ $NH_3$ production and absorption (due to GI bleed, constipation, infection).
- ↓ $NH_3$ removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS).

Treatment: lactulose (↑ $NH_4^+$ generation) and rifaximin (↓ $NH_3$-producing gut bacteria).

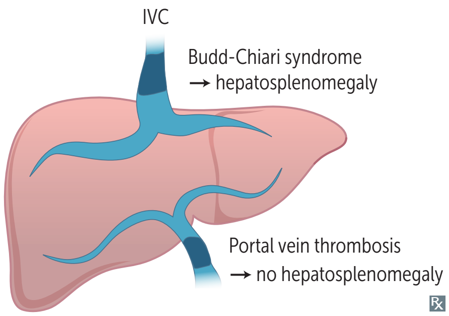
## Liver tumors

| | |
|---|---|
| **Hepatic hemangioma** | Also known as cavernous hemangioma. Most common benign liver tumor (venous malformation) A; typically occurs at age 30–50 years. Biopsy contraindicated because of risk of hemorrhage. |
| **Focal nodular hyperplasia** | Second most common benign liver tumor; occurs predominantly in females aged 35–50 years. Hyperplastic reaction of hepatocytes to an aberrant dystrophic artery. Marked by central stellate scar. Usually asymptomatic and detected incidentally. |
| **Hepatic adenoma** | Rare, benign tumor, often related to oral contraceptive or anabolic steroid use; may regress spontaneously or rupture (abdominal pain and shock). |
| **Hepatocellular carcinoma** | Also known as hepatoma. Most common 1° malignant liver tumor in adults B. Associated with HBV (+/– cirrhosis) and all other causes of cirrhosis (including HCV, alcoholic and nonalcoholic fatty liver disease, autoimmune disease, hemochromatosis, Wilson disease, $\alpha_1$-antitrypsin deficiency) and specific carcinogens (eg, aflatoxin from *Aspergillus*).<br>Findings: anorexia, jaundice, tender hepatomegaly. May lead to decompensation of previously stable cirrhosis (eg, ascites) and Budd-Chiari syndrome. Spreads hematogenously.<br>Diagnosis: ↑ α-fetoprotein; ultrasound or contrast CT/MRI C; biopsy if diagnosis is uncertain |
| **Hepatic angiosarcoma** | Rare, malignant tumor of endothelial origin; associated with exposure to arsenic, vinyl chloride. |
| **Metastases** | Most common malignant liver tumors overall; 1° sources include GI, breast, lung cancers. Metastases are rarely solitary. |

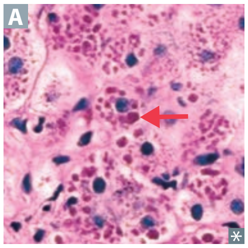



## Budd-Chiari syndrome

Hepatic venous outflow tract obstruction (eg, due to thrombosis, compression) with centrilobular congestion and necrosis → congestive liver disease (hepatomegaly, ascites, varices, abdominal pain, liver failure). Absence of JVD. Associated with hypercoagulable states, polycythemia vera, postpartum state, HCC. May cause nutmeg liver (mottled appearance).



**$\alpha_1$-antitrypsin deficiency**



Misfolded gene product protein aggregates in hepatocellular ER → cirrhosis with PAS ⊕ globules A in liver. Codominant trait.
Often presents in young patients with liver damage and dyspnea without a history of tobacco smoking.

In lungs, ↓ $\alpha_1$-antitrypsin → uninhibited elastase in alveoli → ↓ elastic tissue → panacinar emphysema.

---

**Jaundice**

Abnormal yellowing of the skin and/or sclera A due to bilirubin deposition. Hyperbilirubinemia 2° to ↑ production or ↓ clearance (impaired hepatic uptake, conjugation, excretion).

**HOT Liver**—common causes of ↑ bilirubin level:
**H**emolysis
**O**bstruction
**T**umor
**Liver** disease

**Conjugated (direct) hyperbilirubinemia**

Biliary tract obstruction: gallstones, cholangiocarcinoma, pancreatic or liver cancer, liver fluke.
Biliary tract disease:
- 1° sclerosing cholangitis
- 1° biliary cholangitis

Excretion defect: Dubin-Johnson syndrome, Rotor syndrome.

**Unconjugated (indirect) hyperbilirubinemia**

Hemolytic, physiologic (newborns), Crigler-Najjar, Gilbert syndrome.

**Mixed (direct and indirect) hyperbilirubinemia**

Hepatitis, cirrhosis.

---

**Physiologic neonatal jaundice**

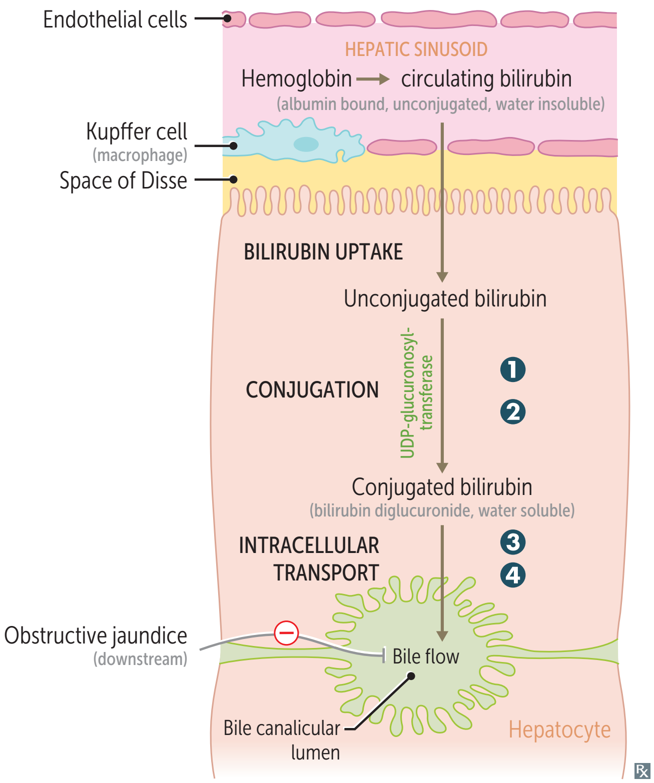
At birth, lower activity of UDP-glucuronosyltransferase → unconjugated hyperbilirubinemia → jaundice/kernicterus (deposition of unconjugated, lipid-soluble bilirubin in the brain, particularly basal ganglia).
Occurs after first 24 hours of life and usually resolves without treatment in 1–2 weeks.
Treatment: phototherapy (non-UV) isomerizes unconjugated bilirubin to water-soluble form.

---

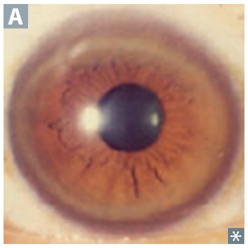
**Biliary atresia**

Most common reason for pediatric liver transplantation.
Fibro-obliterative destruction of bile ducts → cholestasis.
Often presents as a newborn with persistent jaundice after 2 weeks of life, darkening urine, acholic stools, hepatomegaly.
Labs: ↑ direct bilirubin and GGT.

| | |
|---|---|
| **Hereditary hyperbilirubinemias** | All autosomal recessive. |
| **❶ Gilbert syndrome** | Mildly ↓ UDP-glucuronosyltransferase conjugation. Asymptomatic or mild jaundice usually with stress, illness, or fasting. ↑ unconjugated bilirubin without overt hemolysis.<br>Relatively common, benign condition. |
| **❷ Crigler-Najjar syndrome, type I** | Absent UDP-glucuronosyltransferase. Presents early in life, but some patients may not have neurologic signs until later in life.<br>Findings: jaundice, kernicterus (bilirubin deposition in brain), ↑ unconjugated bilirubin.<br>Treatment: plasmapheresis and phototherapy (does not conjugate UCB; but does ↑ polarity and ↑ water solubility to allow excretion). Liver transplant is curative.<br>Type II is less severe and responds to phenobarbital, which ↑ liver enzyme synthesis. |
| **❸ Dubin-Johnson syndrome** | Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black (**D**ark) liver due to impaired excretion of epinephrine metabolites. Benign. |
| **❹ Rotor syndrome** | Phenotypically similar to Dubin-Johnson, but milder in presentation without black (**R**egular) liver. Due to impaired hepatic storage of conjugated bilirubin. |



**Wilson disease**

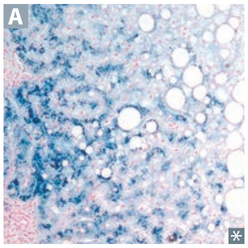


Also called hepatolenticular degeneration. Autosomal recessive mutations in hepatocyte copper-transporting ATPase (*ATP7B* gene; chromosome 13) → ↓ copper incorporation into apoceruloplasmin and excretion into bile → ↓ serum ceruloplasmin. Copper accumulates, especially in liver, brain (eg, basal ganglia), cornea, kidneys; ↑ urine copper.

Presents before age 40 with liver disease (eg, hepatitis, acute liver failure, cirrhosis), neurologic disease (eg, dysarthria, dystonia, tremor, parkinsonism), psychiatric disease, Kayser-Fleischer rings (deposits in Descemet membrane of cornea) A, hemolytic anemia, renal disease (eg, Fanconi syndrome).

Treatment: chelation with penicillamine or trientine, oral zinc. Liver transplant in acute liver failure related to Wilson disease.

**Hemochromatosis**



Autosomal recessive. Mutation in *HFE* gene, located on chromosome 6. Leads to abnormal iron sensing and ↑ intestinal absorption (↑ ferritin, ↑ iron, ↓ TIBC → ↑ transferrin saturation). Iron overload can also be 2° to chronic transfusion therapy (eg, β-thalassemia major). Iron accumulates, especially in liver, pancreas, skin, heart, pituitary, joints. Hemosiderin (iron) can be identified on liver MRI or biopsy with Prussian blue stain A.

Presents after age 40 when total body iron > 20 g; iron loss through menstruation slows progression in females. Classic triad of cirrhosis, diabetes mellitus, skin pigmentation ("bronze diabetes"). Also causes restrictive cardiomyopathy (classic) or dilated cardiomyopathy (reversible), hypogonadism, arthropathy (calcium pyrophosphate deposition; especially metacarpophalangeal joints). HCC is common cause of death.

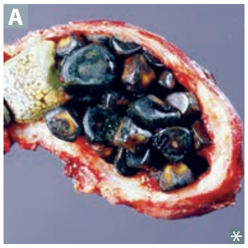
Treatment: repeated phlebotomy, iron (Fe) chelation with deferasirox, deferoxamine, deferiprone.

**Biliary tract disease**

May present with pruritus, jaundice, dark urine, light-colored stool, hepatosplenomegaly. Typically with cholestatic pattern of LFTs (↑ conjugated bilirubin, ↑ cholesterol, ↑ ALP, ↑ GGT).

| | PATHOLOGY | EPIDEMIOLOGY | ADDITIONAL FEATURES |
|---|---|---|---|
| **Primary sclerosing cholangitis** | Unknown cause of concentric "onion skin" bile duct fibrosis → alternating strictures and dilation with "beading" of intra- and extrahepatic bile ducts on ERCP, magnetic resonance cholangiopancreatography (MRCP). | Classically in middle-aged males with ulcerative colitis. | Associated with ulcerative colitis. MPO-ANCA/ p-ANCA ⊕. ↑ IgM. Can lead to 2° biliary cirrhosis. ↑ risk of cholangiocarcinoma and gallbladder cancer. |
| **Primary biliary cholangitis** | Autoimmune reaction → lymphocytic infiltrate +/– granulomas → destruction of lobular bile ducts. | Classically in middle-aged females. | Anti-mitochondrial antibody ⊕, ↑ IgM. Associated with other autoimmune conditions (eg, Hashimoto thyroiditis, rheumatoid arthritis, celiac disease).<br>Treatment: ursodiol. |
| **Secondary biliary cirrhosis** | Extrahepatic biliary obstruction → ↑ pressure in intrahepatic ducts → injury/ fibrosis and bile stasis. | Patients with known obstructive lesions (gallstones, biliary strictures, pancreatic carcinoma). | May be complicated by acute cholangitis. |

## Cholelithiasis and related pathologies



↑ cholesterol and/or bilirubin, ↓ bile salts, and gallbladder stasis all cause stones.

2 types of stones:

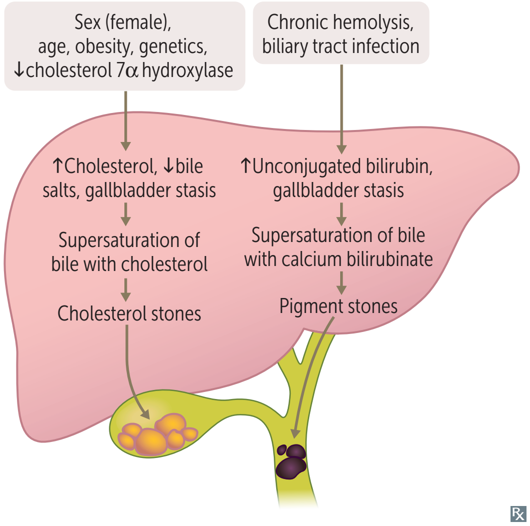
- Cholesterol stones (radiolucent with 10–20% opaque due to calcifications)—80% of stones. Associated with obesity, Crohn disease, advanced age, estrogen therapy, multiparity, rapid weight loss, medications (eg, fibrates).
- Pigment stones A (black = radiopaque, $Ca^{2+}$ bilirubinate, hemolysis; brown = radiolucent, infection). Associated with Crohn disease, chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infections, total parenteral nutrition (TPN).

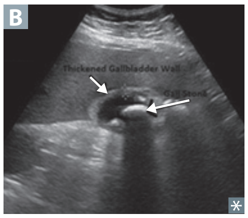
Risk factors (**4 F**'s):

1. **F**emale
2. **F**at (obesity)
3. **F**ertile (multiparity)
4. **F**orty

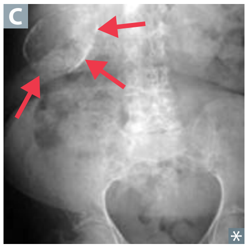
Most common complication is cholecystitis; can also cause acute pancreatitis, acute cholangitis.

Diagnose with ultrasound. Treat with elective cholecystectomy if symptomatic.




| RELATED PATHOLOGIES | CHARACTERISTICS |
|---|---|
| **Biliary colic** | Associated with nausea/vomiting and dull RUQ pain. Neurohormonal activation (eg, by CCK after a fatty meal) triggers contraction of gallbladder, forcing stone into cystic duct. Labs are normal, ultrasound shows cholelithiasis. |
| **Choledocholithiasis** | Presence of gallstone(s) in common bile duct, often leading to elevated ALP, GGT, direct bilirubin, and/or AST/ALT. |
| **Cholecystitis**<br> | Acute or chronic inflammation of gallbladder.<br>Calculous cholecystitis—most common type; due to gallstone impaction in the cystic duct resulting in inflammation and gallbladder wall thickening (arrows in B); can produce 2° infection.<br>Acalculous cholecystitis—due to gallbladder stasis, hypoperfusion, or infection (CMV); seen in critically ill patients.<br>Murphy sign: inspiratory arrest on RUQ palpation due to pain. Pain may radiate to right shoulder (due to irritation of phrenic nerve). ↑ ALP if bile duct becomes involved (eg, acute cholangitis).<br>Diagnose with ultrasound or cholescintigraphy (HIDA scan). Failure to visualize gallbladder on HIDA scan suggests obstruction.<br>Gallstone ileus—fistula between gallbladder and GI tract → stone enters GI lumen → obstructs at ileocecal valve (narrowest point); can see air in biliary tree (pneumobilia). Rigler triad: radiographic findings of pneumobilia, small bowel obstruction, gallstone (usually in iliac fossa). |

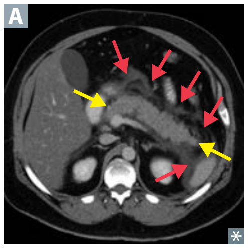
## Cholelithiasis and related pathologies *(continued)*

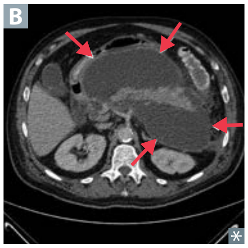
| RELATED PATHOLOGIES | CHARACTERISTICS |
|---|---|
| **Porcelain gallbladder**  | Calcified gallbladder due to chronic cholecystitis; usually found incidentally on imaging C. Treatment: prophylactic cholecystectomy generally recommended due to ↑ risk of gallbladder cancer (mostly adenocarcinoma). |
| **Acute cholangitis** | Also called ascending cholangitis. Infection of biliary tree usually due to obstruction that leads to stasis/bacterial overgrowth.<br>Charcot triad of cholangitis includes jaundice, fever, RUQ pain.<br>Reynolds pentad is Charcot triad plus altered mental status and shock (hypotension). |

**Cholangiocarcinoma**

Malignant tumor of bile duct epithelium. Risk factors include 1° sclerosing cholangitis, liver fluke infections. Usually presents late with fatigue, weight loss, abdominal pain, jaundice. Imaging may show biliary tract obstruction. Histology: infiltrating neoplastic glands associated with desmoplastic stroma.

**Acute pancreatitis**





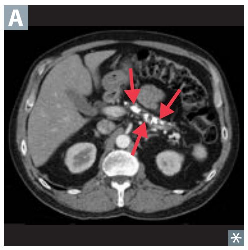
Autodigestion of pancreas by pancreatic enzymes (A shows pancreas [yellow arrows] surrounded by edema [red arrows]).

Causes: **I**diopathic, **G**allstones, **E**thanol, **T**rauma, **S**teroids, **M**umps, **A**utoimmune disease, **S**corpion sting, **H**ypercalcemia/**H**ypertriglyceridemia (> 1000 mg/dL), **E**RCP, **D**rugs (eg, sulfa drugs, NRTIs, protease inhibitors). **I GET SMASHED**.

Diagnosis by 2 of 3 criteria: acute epigastric pain often radiating to the back, ↑ serum amylase or lipase (more specific) to 3× upper limit of normal, or characteristic imaging findings.

Complications: pseudocyst B (lined by granulation tissue, not epithelium), abscess, necrosis, hemorrhage, infection, organ failure (ALI/ARDS, shock, renal failure), hypocalcemia (precipitation of $Ca^{2+}$ soaps).

**Chronic pancreatitis**

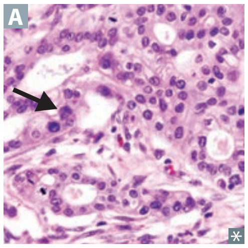


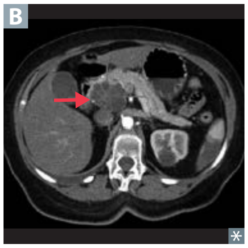
Chronic inflammation, atrophy, calcification of the pancreas A. Major risk factors include alcohol use disorder and genetic predisposition (eg, cystic fibrosis); can be idiopathic. Complications include pancreatic insufficiency and pseudocysts.

Pancreatic insufficiency (typically when <10% pancreatic function) may manifest with steatorrhea, fat-soluble vitamin deficiency, diabetes mellitus.

Amylase and lipase may or may not be elevated (almost always elevated in acute pancreatitis).

**Pancreatic adenocarcinoma**





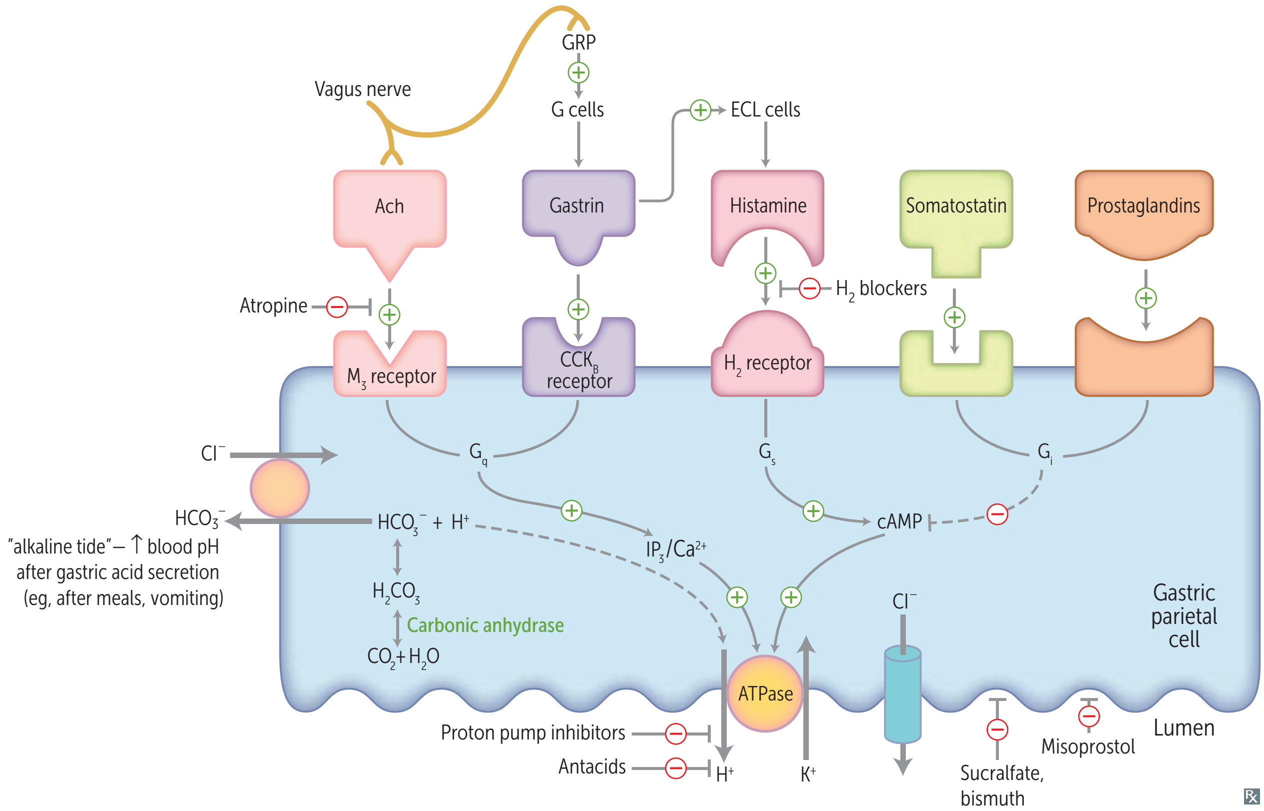
Very aggressive tumor arising from pancreatic ducts (disorganized glandular structure with cellular infiltration A); often metastatic at presentation, with average survival ~ 1 year after diagnosis. Tumors more common in pancreatic head B (lead to obstructive jaundice). Associated with CA 19-9 tumor marker (also CEA, less specific).

Risk factors:
- Tobacco smoking
- Chronic pancreatitis (especially > 20 years)
- Diabetes
- Age > 50 years

Often presents with:
- Abdominal pain radiating to back
- Weight loss (due to malabsorption and anorexia)
- Migratory thrombophlebitis—redness and tenderness on palpation of extremities (Trousseau syndrome)
- Obstructive jaundice with palpable, nontender gallbladder (Courvoisier sign)

## ▶ GASTROINTESTINAL—PHARMACOLOGY

### Acid suppression therapy



| | | |
|---|---|---|
| **$H_2$-blockers** | Cimetidine, famotidine, nizatidine. | Take $H_2$ blockers before you **dine**. Think "**table for 2**" to remember **$H_2$**. |
| MECHANISM | Reversible block of histamine $H_2$-receptors → ↓ $H^+$ secretion by parietal cells. | |
| CLINICAL USE | Peptic ulcer, gastritis, mild esophageal reflux. | |
| ADVERSE EFFECTS | Cimetidine is a potent inhibitor of cytochrome P-450 (multiple drug interactions); it also has antiandrogenic effects (prolactin release, gynecomastia, impotence, ↓ libido in males); can cross blood-brain barrier (confusion, dizziness, headaches) and placenta. Cimetidine ↓ renal excretion of creatinine. Other $H_2$ blockers are relatively free of these effects. | |

| | |
|---|---|
| **Proton pump inhibitors** | Omeprazole, lansoprazole, esomeprazole, pantoprazole, dexlansoprazole. |
| MECHANISM | Irreversibly inhibit $H^+/K^+$ ATPase in stomach parietal cells. |
| CLINICAL USE | Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome, component of therapy for *H pylori*, stress ulcer prophylaxis. |
| ADVERSE EFFECTS | ↑ risk of *C difficile* infection, pneumonia, acute interstitial nephritis. Vitamin $B_{12}$ malabsorption; ↓ serum $Mg^{2+}$ and ↓ $Ca^{2+}$ absorption (potentially leading to increased fracture risk in elderly). |

| | | |
|---|---|---|
| **Antacids** | Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying.<br>All can cause hypokalemia.<br>Overuse can also cause the following problems: | |
| **Aluminum hydroxide** | **C**onstipation, **H**ypophosphatemia, **O**steodystrophy, **P**roximal muscle weakness, **S**eizures | Alu**minimum** amount of feces<br>**CHOPS** |
| **Calcium carbonate** | Hypercalcemia (milk-alkali syndrome), rebound acid ↑ | Can chelate and ↓ effectiveness of other drugs (eg, tetracycline) |
| **Magnesium hydroxide** | Diarrhea, hyporeflexia, hypotension, cardiac arrest | **$Mg^{2+}$** = **M**ust **go 2** the bathroom |

| | |
|---|---|
| **Bismuth, sucralfate** | |
| MECHANISM | Bind to ulcer base, providing physical protection and allowing $HCO_3^-$ secretion to reestablish pH gradient in the mucous layer. Sucralfate requires acidic environment, not given with PPIs/$H_2$ blockers. |
| CLINICAL USE | ↑ ulcer healing, travelers' diarrhea (bismuth). Bismuth also used in quadruple therapy for *H pylori* gastritis. |

| | |
|---|---|
| **Misoprostol** | |
| MECHANISM | $PGE_1$ analog. ↑ production and secretion of gastric mucous barrier, ↓ acid production. |
| CLINICAL USE | Prevention of NSAID-induced peptic ulcers (NSAIDs block $PGE_1$ production). Also used off-label for induction of labor (ripens cervix). |
| ADVERSE EFFECTS | Diarrhea. Contraindicated in patients of childbearing potential (abortifacient). |

## Octreotide

| | |
|---|---|
| MECHANISM | Long-acting somatostatin analog; inhibits secretion of various splanchnic vasodilatory hormones. |
| CLINICAL USE | Acute variceal bleeds, acromegaly, VIPoma, carcinoid tumors. |
| ADVERSE EFFECTS | Nausea, cramps, steatorrhea. ↑ risk of cholelithiasis due to CCK inhibition. |

## Sulfasalazine

| | |
|---|---|
| MECHANISM | A combination of sulfapyridine (antibacterial) and 5-aminosalicylic acid (anti-inflammatory). Activated by colonic bacteria. |
| CLINICAL USE | Ulcerative colitis, Crohn disease (colitis component). |
| ADVERSE EFFECTS | Malaise, nausea, sulfonamide toxicity, reversible oligospermia. |

## Loperamide

| | |
|---|---|
| MECHANISM | Agonist at μ-opioid receptors; slows gut motility. Poor CNS penetration (low addictive potential). |
| CLINICAL USE | Diarrhea. |
| ADVERSE EFFECTS | Constipation, nausea. |

## Ondansetron

| | |
|---|---|
| MECHANISM | 5-$HT_3$ antagonist. Acts peripherally (↓ vagal stimulation) and centrally. Potent antiemetic. |
| CLINICAL USE | Control vomiting postoperatively and in patients undergoing cancer chemotherapy. |
| ADVERSE EFFECTS | Headache, constipation, QT interval prolongation, serotonin syndrome. |

## Aprepitant

| | |
|---|---|
| MECHANISM | Substance P antagonist. Blocks $NK_1$ (neurokinin-1) receptors in brain. |
| CLINICAL USE | Antiemetic for chemotherapy-induced nausea and vomiting. |

## Metoclopramide

| | |
|---|---|
| MECHANISM | $D_2$ receptor antagonist. ↑ resting tone, contractility, LES tone, motility, promotes gastric emptying. Does not influence colon transport time. |
| CLINICAL USE | Diabetic and postoperative gastroparesis, antiemetic, persistent GERD. |
| ADVERSE EFFECTS | ↑ parkinsonian effects, tardive dyskinesia. Restlessness, drowsiness, fatigue, depression, diarrhea. Drug interaction with digoxin and diabetic agents. Contraindicated in patients with small bowel obstruction, Parkinson disease (due to $D_2$-receptor blockade), ↓ seizure threshold. |

## Orlistat

| | |
|---|---|
| MECHANISM | Inhibits gastric and pancreatic lipase → ↓ breakdown and absorption of dietary fats. Taken with fat-containing meals. |
| CLINICAL USE | Weight loss. |
| ADVERSE EFFECTS | Abdominal pain, flatulence, bowel urgency/frequent bowel movements, steatorrhea; ↓ absorption of fat-soluble vitamins. |

## Laxatives

Indicated for constipation or patients on opiates requiring a bowel regimen.

| | EXAMPLES | MECHANISM | ADVERSE EFFECTS |
|---|---|---|---|
| **Bulk-forming laxatives** | Psyllium, methylcellulose | Soluble fibers draw water into gut lumen, forming a viscous liquid that promotes peristalsis | Bloating |
| **Osmotic laxatives** | Magnesium hydroxide, magnesium citrate, polyethylene glycol, lactulose | Provides osmotic load to draw water into GI lumen<br>Lactulose also treats hepatic encephalopathy: gut flora degrade lactulose into metabolites (lactic acid, acetic acid) that promote nitrogen excretion as $NH_4^+$ | Diarrhea, dehydration; may be misused by patients with bulimia nervosa; overuse may cause metabolic alkalosis |
| **Stimulants** | Senna, bisacodyl | Enteric nerve stimulation → colonic contraction | Diarrhea, melanosis coli; overuse may cause metabolic alkalosis |
| **Emollients** | Docusate | Promotes incorporation of water and fat into stool | Diarrhea; overuse may cause metabolic alkalosis |

NOTES

HIGH-YIELD SYSTEMS

# Hematology and Oncology

*"You're always somebody's type! (blood type, that is)"*

—BloodLink

*"The best blood will at some time get into a fool or a mosquito."*

—Austin O'Malley

*"A life touched by cancer is not a life destroyed by cancer."*

—Drew Boswell, *Climbing the Cancer Mountain*

*"Without hair, a queen is still a queen."*

—Prajakta Mhadnak

*"Blood can circulate forever if you keep donating it."*

—Anonymous

When studying hematology, pay close attention to the many cross connections to immunology. Make sure you master the different types of anemias. Be comfortable interpreting blood smears. When reviewing oncologic drugs, focus on mechanisms and adverse effects rather than details of clinical uses, which may be lower yield.

Please note that solid tumors are covered in their respective organ system chapters.

## ▶ HEMATOLOGY AND ONCOLOGY—EMBRYOLOGY

**Fetal erythropoiesis**

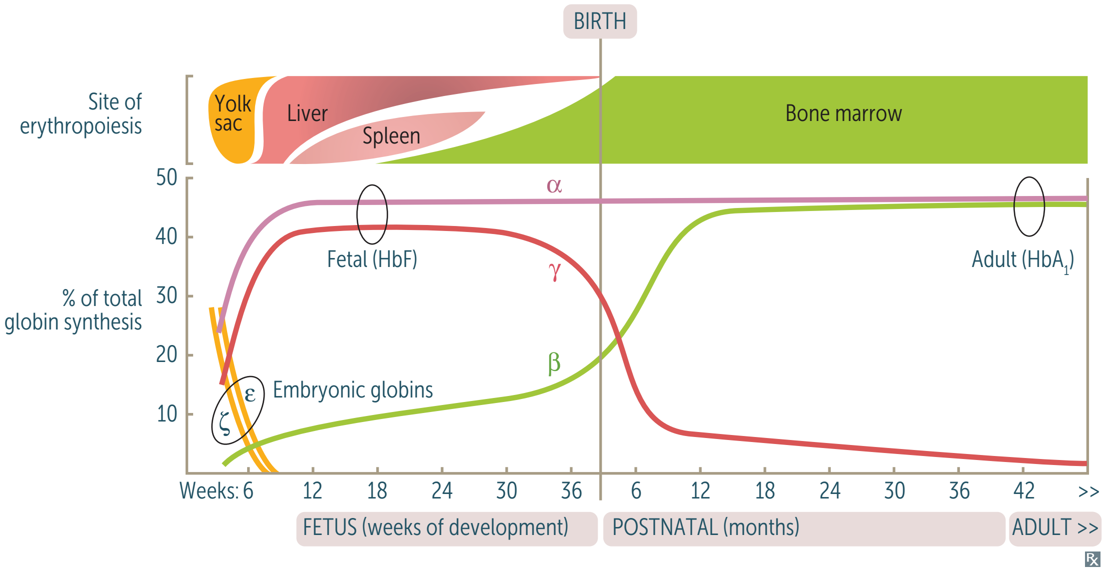
Fetal erythropoiesis occurs in:
- Yolk sac (3–8 weeks)
- Liver (6 weeks–birth)
- Spleen (10–28 weeks)
- Bone marrow (18 weeks to adult)

Young liver synthesizes blood.

**Hemoglobin development**

Embryonic globins: ζ and ε.
Fetal hemoglobin (HbF) = $\alpha_2\gamma_2$.
Adult hemoglobin ($HbA_1$) = $\alpha_2\beta_2$.
HbF has higher affinity for $O_2$ due to less avid binding of 2,3-BPG, allowing HbF to extract $O_2$ from maternal hemoglobin ($HbA_1$ and $HbA_2$) across the placenta. $HbA_2$ ($\alpha_2\delta_2$) is a form of adult hemoglobin present in small amounts.

From fetal to adult hemoglobin:
Alpha always; gamma goes, becomes beta.



## Blood groups

| | ABO classification | | | | Rh classification | |
|---|---|---|---|---|---|---|
| | A | B | AB | O | Rh$\oplus$ | Rh$\ominus$ |
| RBC type | A | B | AB | O | | |
| Group antigens on RBC surface | A | B | A & B | None | Rh (D) | None |
| Antibodies in plasma | Anti-B<br>IgM | Anti-A<br>IgM | None | Anti-A Anti-B<br>IgG (predominantly), IgM | None | Anti-D<br>IgG |
| **Clinical relevance** | | | | | | |
| Compatible RBC types to receive | A, O | B, O | AB, A, B, O | O | Rh$\oplus$, Rh$\ominus$ | Rh$\ominus$ |
| Compatible RBC types to donate to | A, AB | B, AB | AB | A, B, AB, O | Rh$\oplus$ | Rh$\oplus$, Rh$\ominus$ |

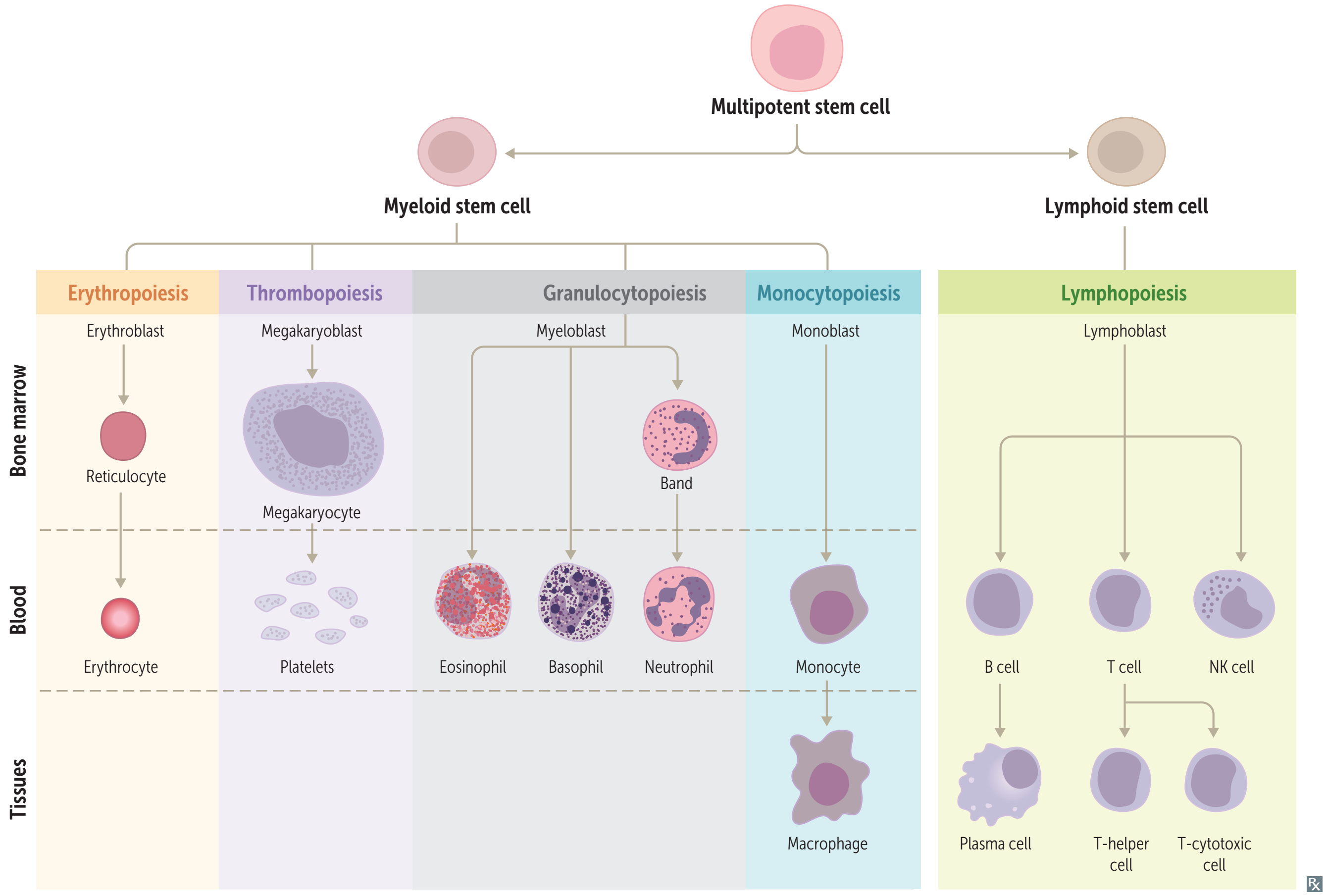
## Hemolytic disease of the fetus and newborn

Also known as erythroblastosis fetalis.

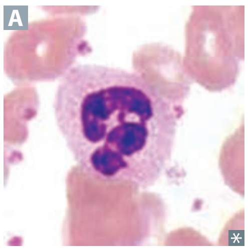
| | Rh hemolytic disease | ABO hemolytic disease |
|---|---|---|
| INTERACTION | Rh $\ominus$ pregnant patient; Rh $\oplus$ fetus. | Type O pregnant patient; type A or B fetus. |
| MECHANISM | First pregnancy: patient exposed to fetal blood (often during delivery) → formation of maternal anti-D IgG.<br>Subsequent pregnancies: anti-D IgG crosses placenta → attacks fetal and newborn RBCs → hemolysis. | Preexisting pregnant patient anti-A and/or anti-B IgG antibodies cross the placenta → attack fetal and newborn RBCs → hemolysis. |
| PRESENTATION | Hydrops fetalis, jaundice shortly after birth, kernicterus. | Mild jaundice in the neonate within 24 hours of birth. Unlike Rh hemolytic disease, can occur in firstborn babies and is usually less severe. |
| TREATMENT/PREVENTION | Prevent by administration of anti-D IgG to Rh $\ominus$ pregnant patients during third trimester and early postpartum period (if fetus Rh $\oplus$). Prevents maternal anti-D IgG production. | Treatment: phototherapy or exchange transfusion. |

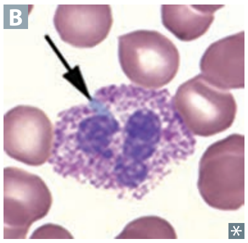
## ▶ HEMATOLOGY AND ONCOLOGY—ANATOMY

### Hematopoiesis




### Neutrophils




Acute inflammatory response cells. Phagocytic. Multilobed nucleus A. Specific granules contain leukocyte alkaline phosphatase (LAP), collagenase, lysozyme, and lactoferrin. Azurophilic granules (lysosomes) contain proteinases, acid phosphatase, myeloperoxidase, and β-glucuronidase.

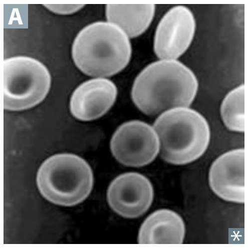
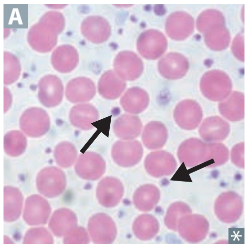
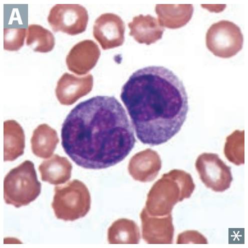
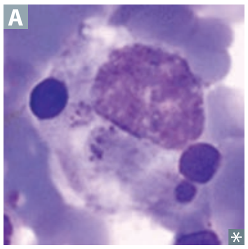
Inflammatory states (eg, bacterial infection) cause neutrophilia and changes in neutrophil morphology, such as left shift, toxic granulation (dark blue, coarse granules), Döhle bodies (light blue, peripheral inclusions, arrow in B), and cytoplasmic vacuoles.

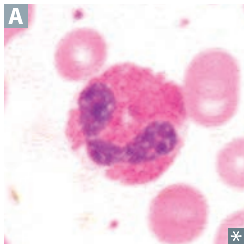
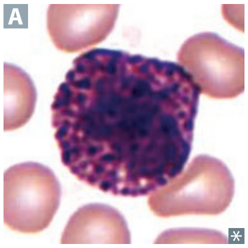
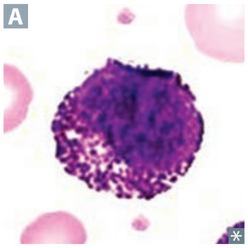
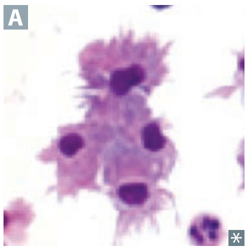
Neutrophil chemotactic agents: C5a, IL-8, $LTB_4$, 5-HETE (leukotriene precursor), kallikrein, platelet-activating factor, *N*-formylmethionine (bacterial proteins).

Hypersegmented neutrophils (nucleus has 6+ lobes) are seen in vitamin $B_{12}$/folate deficiency.

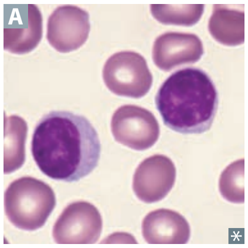
Left shift—↑ neutrophil precursors (eg, band cells, metamyelocytes) in peripheral blood. Reflects states of ↑ myeloid proliferation (eg, inflammation, CML).

Leukoerythroblastic reaction—left shift accompanied by immature RBCs. Suggests bone marrow infiltration (eg, myelofibrosis, metastasis).

| | | |
|---|---|---|
| **Erythrocytes**  | Carry $O_2$ to tissues and $CO_2$ to lungs. Anucleate and lack organelles; biconcave A, with large surface area-to-volume ratio for rapid gas exchange. Life span of ~120 days in healthy adults; 60-90 days in neonates. Source of energy is glucose (90% used in glycolysis, 10% used in HMP shunt). Membranes contain $Cl^-/HCO_3^-$ antiporter, which allow RBCs to export $HCO_3^-$ and transport $CO_2$ from the periphery to the lungs for elimination. | *Erythro* = red; *cyte* = cell.<br>Erythrocytosis = polycythemia = ↑ Hct.<br>Anisocytosis = varying sizes.<br>Poikilocytosis = varying shapes.<br>Reticulocyte = immature RBC; reflects erythroid proliferation.<br>Bluish color (polychromasia) on Wright-Giemsa stain of reticulocytes represents residual ribosomal RNA. |
| **Thrombocytes (platelets)**  | Involved in 1° hemostasis. Anucleate, small cytoplasmic fragments A derived from megakaryocytes. Life span of 8–10 days (pl8lets). When activated by endothelial injury, aggregate with other platelets and interact with fibrinogen to form platelet plug. Contain dense granules ($Ca^{2+}$, ADP, Serotonin, Histamine; CASH) and α granules (vWF, fibrinogen, fibronectin, platelet factor 4). Approximately ⅓ of platelet pool is stored in the spleen. | Thrombocytopenia or ↓ platelet function results in petechiae.<br>vWF receptor: GpIb.<br>Fibrinogen receptor: GpIIb/IIIa.<br>Thrombopoietin stimulates megakaryocyte proliferation.<br>Alfa granules contain vWF, fibrinogen, fibronectin, platelet factor four. |
| **Monocytes**  | Found in blood, differentiate into macrophages in tissues.<br>Large, kidney-shaped nucleus A. Extensive "frosted glass" cytoplasm. | *Mono* = one (nucleus); *cyte* = cell. |
| **Macrophages**  | Phagocytose bacteria, cellular debris, and senescent RBCs. Long life in tissues. Differentiate from circulating blood monocytes A. Activated by γ-interferon. Can function as antigen-presenting cell via MHC II. Important cellular component of granulomas (eg, TB, sarcoidosis), where they may fuse to form giant cells. | *Macro* = large; *phage* = eater.<br>Macrophage naming varies by specific tissue type (eg, Kupffer cells in liver, histiocytes in connective tissue, Langerhans cells in skin, osteoclasts in bone, microglial cells in brain).<br>Lipid A from bacterial LPS binds CD14 on macrophages to initiate septic shock. |

| | | |
|---|---|---|
| **Eosinophils**<br>A<br> | Defend against helminthic infections (major basic protein). Bilobate nucleus. Packed with large eosinophilic granules of uniform size A. Highly phagocytic for antigen-antibody complexes.<br>Produce histaminase, major basic protein (MBP, a helminthotoxin), eosinophil peroxidase, eosinophil cationic protein, and eosinophil-derived neurotoxin. | *Eosin* = pink dye; *philic* = loving.<br>Causes of eosinophilia (**PACMAN E**ats):<br>**P**arasites<br>**A**sthma<br>**C**hronic adrenal insufficiency<br>**M**yeloproliferative disorders<br>**A**llergic processes<br>**N**eoplasia (eg, Hodgkin lymphoma)<br>**E**osinophilic granulomatosis with polyangiitis |
| **Basophils**<br>A<br> | Mediate allergic reaction. Densely basophilic granules A contain heparin (anticoagulant) and histamine (vasodilator). Leukotrienes synthesized and released on demand. | **Baso**philic—stains readily with **basic** stains.<br>Basophilia is uncommon, but can be a sign of myeloproliferative disorders, particularly CML. |
| **Mast cells**<br>A<br> | Mediate local tissue allergic reactions. Contain basophilic granules A. Originate from same precursor as basophils but are not the same cell type. Can bind the Fc portion of IgE to membrane. Activated by tissue trauma, C3a and C5a, surface IgE cross-linking by antigen (IgE receptor aggregation) → degranulation → release of histamine, heparin, tryptase, and eosinophil chemotactic factors. | Involved in type I hypersensitivity reactions.<br>Cromolyn sodium prevents mast cell degranulation (used for asthma prophylaxis).<br>Vancomycin, opioids, and radiocontrast dye can elicit IgE-independent mast cell degranulation.<br>Mastocytosis—rare; proliferation of mast cells in skin and/or extracutaneous organs. Associated with c-*KIT* mutations and ↑ serum tryptase. ↑ histamine → flushing, pruritus, hypotension, abdominal pain, diarrhea, peptic ulcer disease. |
| **Dendritic cells**<br>A<br> | Highly phagocytic antigen-presenting cells (APCs) A. Function as link between innate and adaptive immune systems. Express MHC class II and Fc receptors on surface. Can present exogenous antigens on MHC class I (cross-presentation). | |

## Lymphocytes




Refer to B cells, T cells, and NK cells. B cells and T cells mediate adaptive immunity. NK cells are part of the innate immune response. Round, densely staining nucleus with small amount of pale cytoplasm A.

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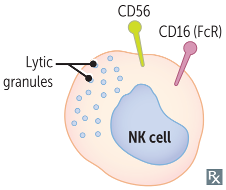
## Natural killer cells




Important in innate immunity, especially against intracellular pathogens. Larger than B and T cells, with distinctive cytoplasmic lytic granules (containing perforin and granzymes) that, when released, act on target cells to induce apoptosis. Distinguish between healthy and infected cells by identifying cell surface proteins (induced by stress, malignant transformation, or microbial infections).

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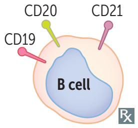
## B cells




Mediate humoral immune response. Originate from stem cells in bone marrow and matures in marrow. Migrate to peripheral lymphoid tissue (follicles of lymph nodes, white pulp of spleen, unencapsulated lymphoid tissue). When antigen is encountered, B cells differentiate into plasma cells (which produce antibodies) and memory cells. Can function as an APC.

B = bone marrow.

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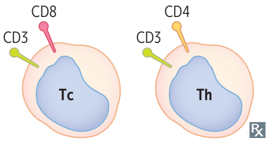
## T cells




Mediate cellular immune response. Originate from stem cells in the bone marrow, but mature in the thymus. Differentiate into cytotoxic T cells (express CD8, recognize MHC I), helper T cells (express CD4, recognize MHC II), and regulatory T cells. CD28 (costimulatory signal) necessary for T-cell activation. Most circulating lymphocytes are T cells (80%).

T = thymus.

CD4+ helper T cells are the primary target of HIV.

Rule of 8: MHC II × CD4 = 8; MHC I × CD8 = 8.

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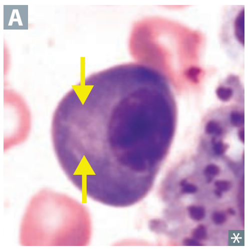
## Plasma cells

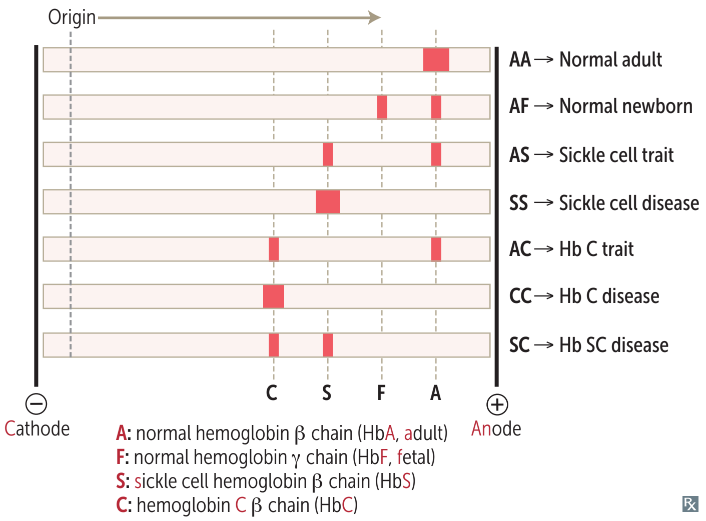



Produce large amounts of antibody specific to a particular antigen. "Clock-face" chromatin distribution and eccentric nucleus, abundant RER, and well-developed Golgi apparatus (arrows in A). Found in bone marrow and normally do not circulate in peripheral blood.

Multiple myeloma is a plasma cell dyscrasia.

## ▶ HEMATOLOGY AND ONCOLOGY—PHYSIOLOGY

### Hemoglobin electrophoresis




On a gel, hemoglobin migrates from the negatively charged cathode to the positively charged anode. HbA migrates the farthest, followed by HbF, HbS, and HbC. This is because the missense mutations in HbS and HbC replace glutamic acid ⊖ with valine (neutral) and lysine ⊕, respectively, making HbC and HbS more positively charged than HbA.

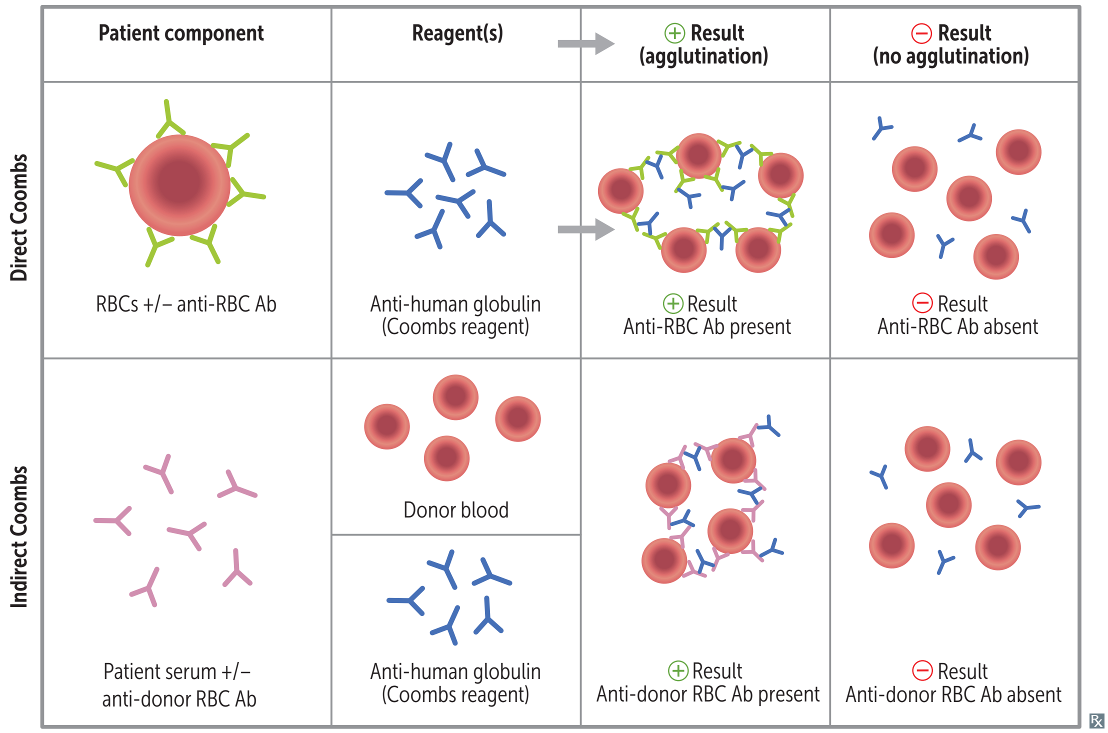
A Fat Santa Claus can't (cathode → anode) go far.

### Coombs test

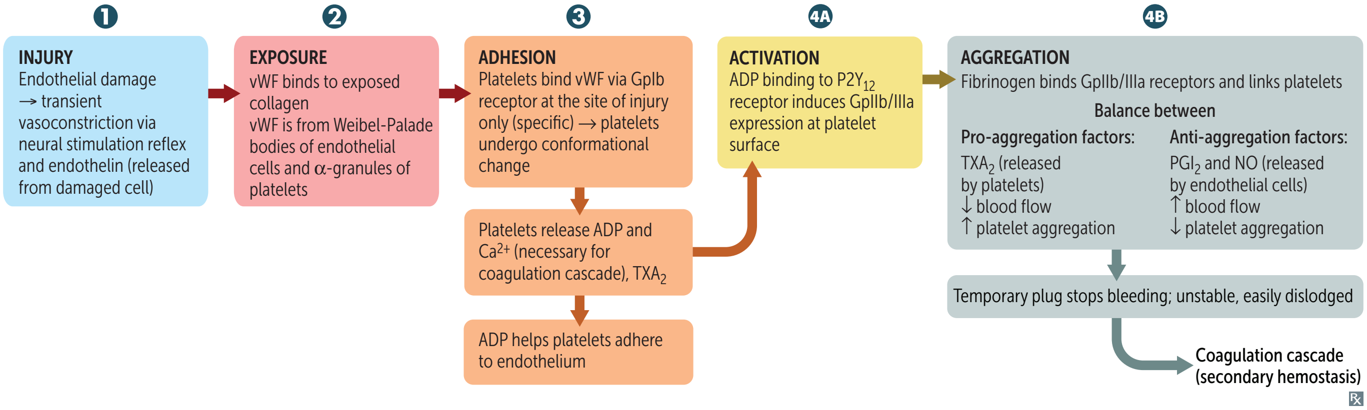
Also called antiglobulin test. Detects the presence of antibodies against circulating RBCs.

Direct Coombs test—anti-Ig antibody (Coombs reagent) added to patient's RBCs. RBCs agglutinate if RBCs are coated with Ig. Used for AIHA diagnosis.

Indirect Coombs test—normal RBCs added to patient's serum. If serum has anti-RBC surface Ig, RBCs agglutinate when Coombs reagent is added. Used for pretransfusion testing.



## Platelet plug formation (primary hemostasis)




## Thrombogenesis

Formation of insoluble fibrin mesh.

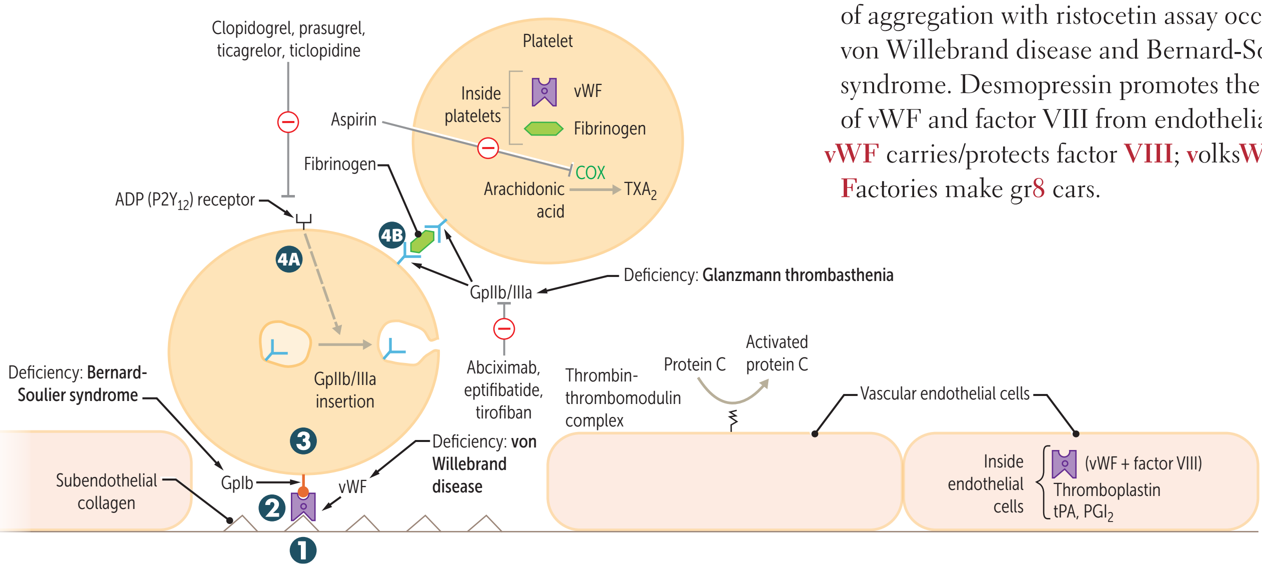
Aspirin irreversibly inhibits cyclooxygenase, thereby inhibiting $TXA_2$ synthesis.

Clopidogrel, prasugrel, ticagrelor, and ticlopidine inhibit ADP-induced expression of GpIIb/IIIa by blocking $P2Y_{12}$ receptor.

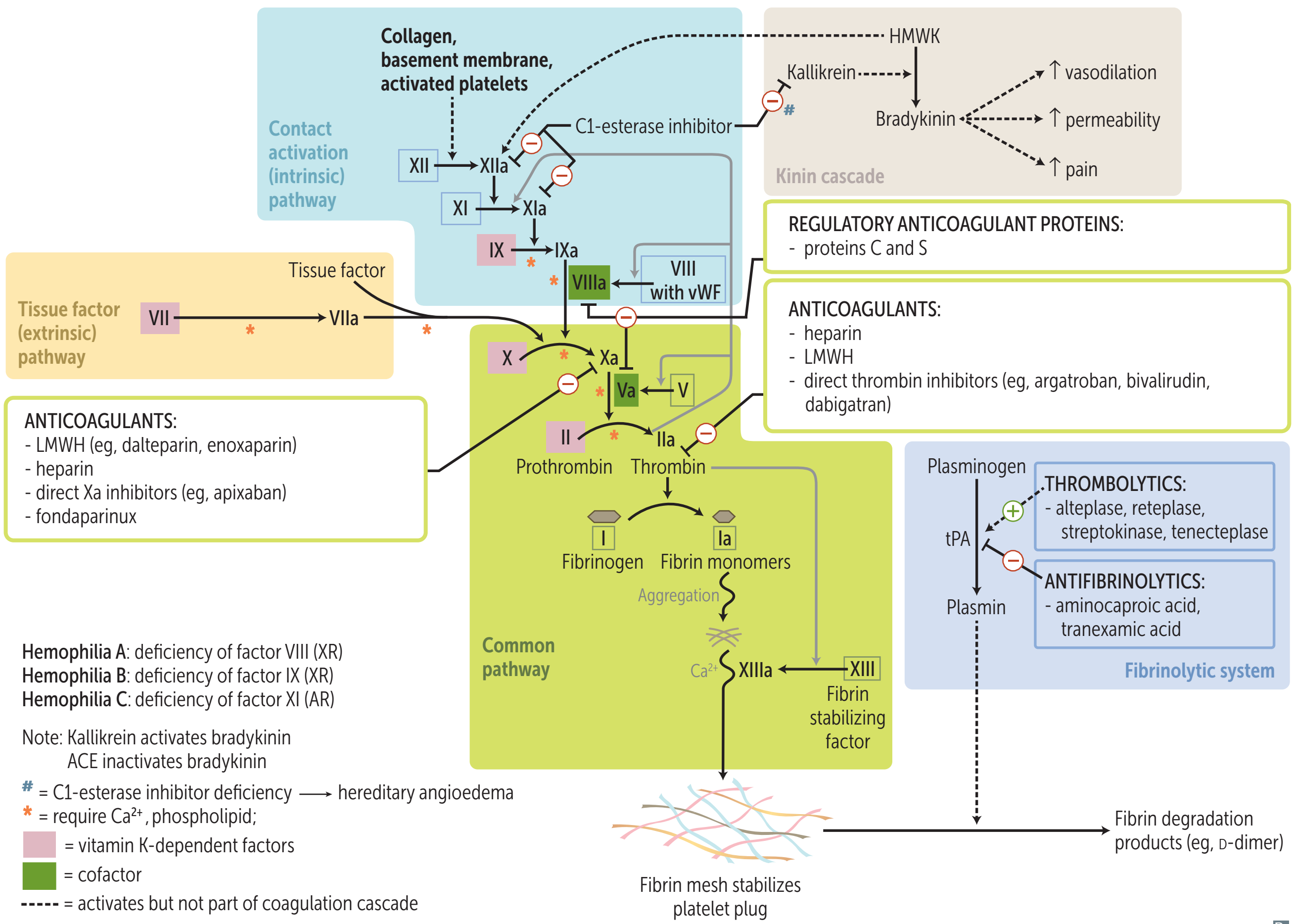
Abciximab, eptifibatide, and tirofiban inhibit GpIIb/IIIa directly.

Ristocetin activates vWF to bind GpIb. Failure of aggregation with ristocetin assay occurs in von Willebrand disease and Bernard-Soulier syndrome. Desmopressin promotes the release of vWF and factor VIII from endothelial cells.

**vWF** carries/protects factor **VIII**; **v**olks**W**agen **F**actories make gr**8** cars.



## Coagulation and kinin pathways



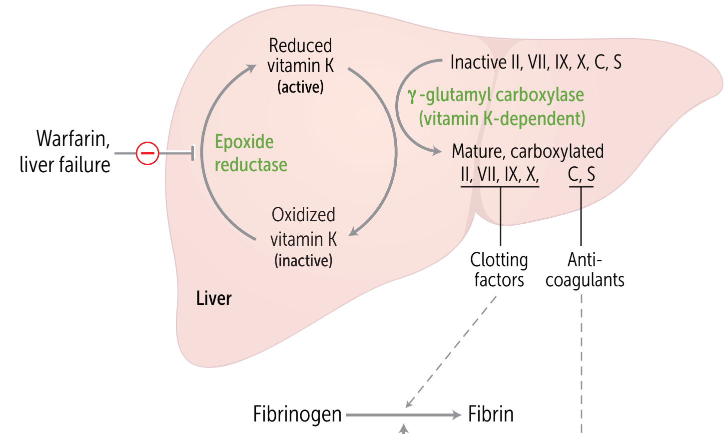

**Hemophilia A**: deficiency of factor VIII (XR)
**Hemophilia B**: deficiency of factor IX (XR)
**Hemophilia C**: deficiency of factor XI (AR)

Note: Kallikrein activates bradykinin
ACE inactivates bradykinin

# = C1-esterase inhibitor deficiency ⟶ hereditary angioedema
* = require $Ca^{2+}$, phospholipid;
= vitamin K-dependent factors
= cofactor
----- = activates but not part of coagulation cascade
LMWH = low-molecular-weight heparin

## Vitamin K–dependent coagulation

### Procoagulation




Vitamin K deficiency—↓ synthesis of factors II, VII, IX, X, protein C, protein S.

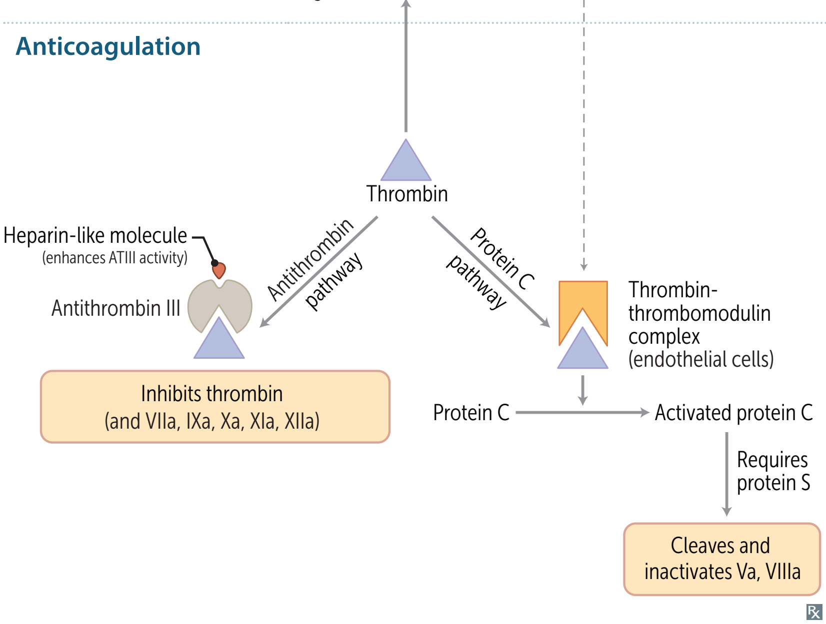
Warfarin inhibits vitamin K epoxide reductase. Vitamin K administration can potentially reverse inhibitory effect of warfarin on clotting factor synthesis (delayed). FFP or PCC administration reverses action of warfarin immediately and can be given with vitamin K in cases of severe bleeding.

Neonates lack enteric bacteria, which produce vitamin K. Early administration of vitamin K overcomes neonatal deficiency/coagulopathy.

Factor VII (seven)—shortest half-life.

Factor II (two)—longest (too long) half-life.

### Anticoagulation




Antithrombin inhibits thrombin (factor IIa) and factors VIIa, IXa, Xa, XIa, XIIa.

Heparin enhances the activity of antithrombin.

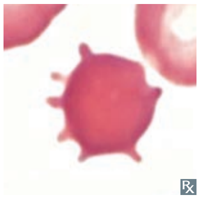
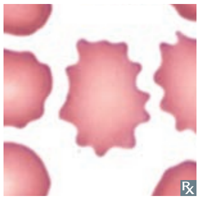
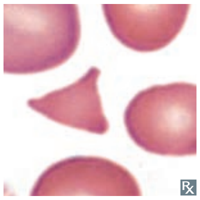
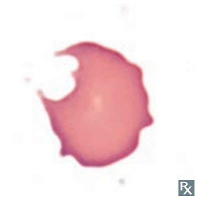
Principal targets of antithrombin: thrombin and factor Xa.

Factor V Leiden mutation produces a factor V resistant to inhibition by activated protein C.

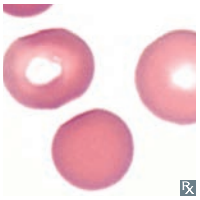
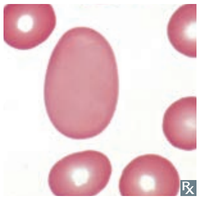
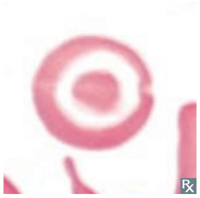
tPA is used clinically as a thrombolytic.

## ▶ HEMATOLOGY AND ONCOLOGY—PATHOLOGY

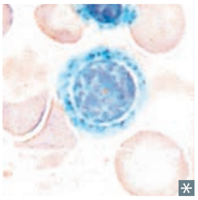
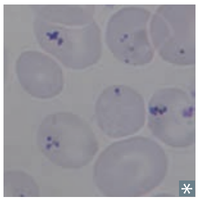
### RBC morphology

| TYPE | EXAMPLE | ASSOCIATED PATHOLOGY | NOTES |
|---|---|---|---|
| **Acanthocytes ("spur cells")** |  | Liver disease, abetalipoproteinemia, vitamin E deficiency | Projections of varying size at irregular intervals (**a**canthocytes are **a**symmetric). |
| **Echinocytes ("burr cells")** |  | Liver disease, ESRD, pyruvate kinase deficiency | Smaller and more uniform projections than acanthocytes (**e**chinocytes are **e**ven). |
| **Dacrocytes ("teardrop cells")** |  | Bone marrow infiltration (eg, myelofibrosis) | RBC "sheds a **tear**" because it's mechanically squeezed out of its home in the bone marrow |
| **Schistocytes** (eg, "helmet" cells) |  | MAHAs (eg, DIC, TTP/HUS, HELLP syndrome), mechanical hemolysis (eg, heart valve prosthesis) | Fragmented RBCs |
| **Degmacytes ("bite cells")** |  | G6PD deficiency | Due to removal of Heinz bodies by splenic macrophages (they "**deg**" them out of/**bite** them off of RBCs) |
| **Elliptocytes** |  | Hereditary elliptocytosis | Caused by mutation in genes encoding RBC membrane proteins (eg, spectrin) |

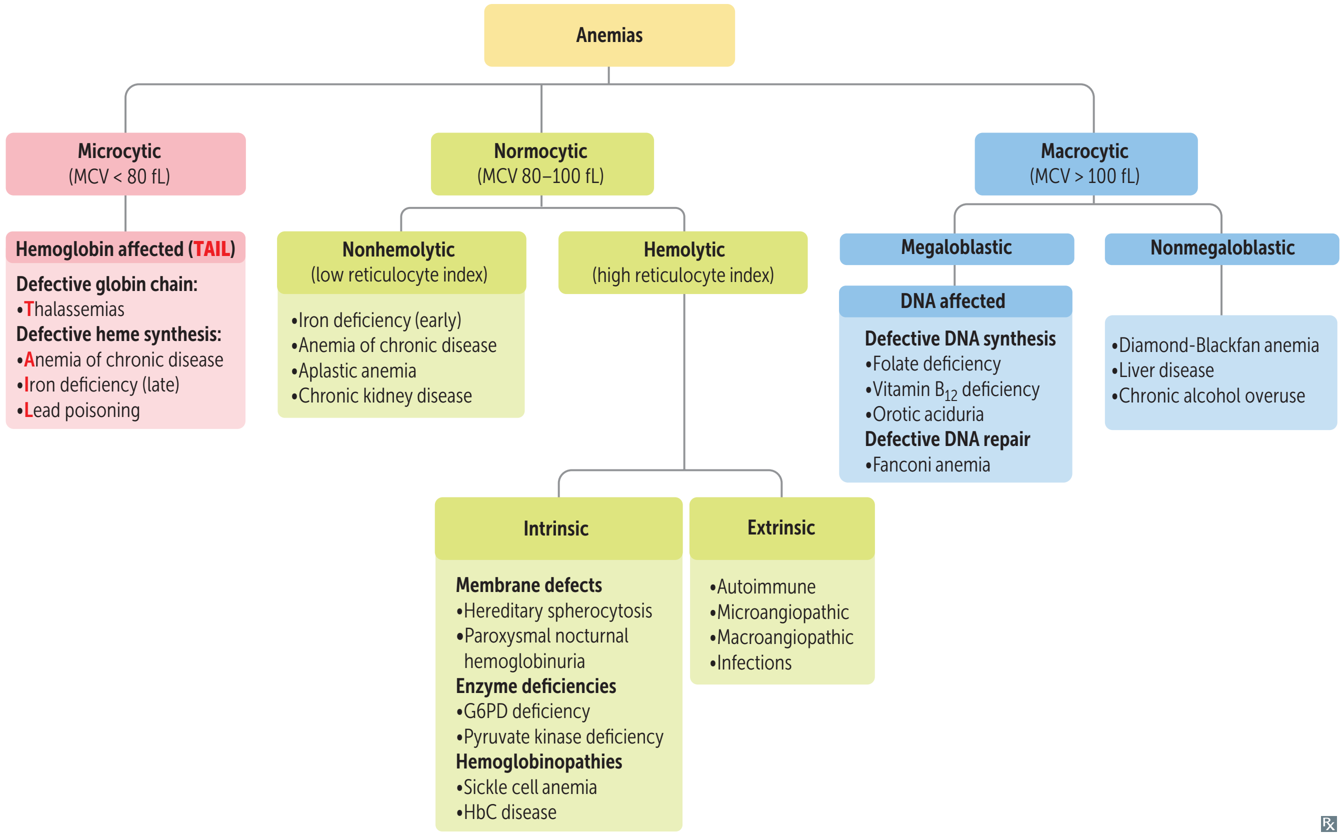
## RBC morphology *(continued)*

| TYPE | EXAMPLE | ASSOCIATED PATHOLOGY | NOTES |
|---|---|---|---|
| **Spherocytes** |  | Hereditary spherocytosis, autoimmune hemolytic anemia | Small, spherical cells without central pallor<br>↓ surface area-to-volume ratio |
| **Macro-ovalocytes** |  | Megaloblastic anemia (also hypersegmented PMNs) | |
| **Target cells** |  | **H**bC disease, **A**splenia, **L**iver disease, **T**halassemia | "**HALT**," said the hunter to his **target**<br>↑ surface area-to-volume ratio |
| **Sickle cells** |  | Sickle cell anemia | Sickling occurs with low $O_2$ conditions (eg, high altitude, acidosis) |

## RBC inclusions

| TYPE | EXAMPLE | ASSOCIATED PATHOLOGY | NOTES |
|---|---|---|---|
| **Bone marrow** | | | |
| **Iron granules** |  | Sideroblastic anemias (eg, lead poisoning, myelodysplastic syndromes, chronic alcohol overuse) | Perinuclear mitochondria with excess iron (forming ring in ringed sideroblasts)<br>Require Prussian blue stain to be visualized |
| **Peripheral smear** | | | |
| **Howell-Jolly bodies** |  | Functional hyposplenia (eg, sickle cell disease), asplenia | Basophilic nuclear remnants (do not contain iron)<br>Usually removed by splenic macrophages |
| **Basophilic stippling** |  | Sideroblastic anemias, thalassemias | Basophilic ribosomal precipitates (do not contain iron) |
| **Pappenheimer bodies** |  | Sideroblastic anemia | Basophilic granules (contain iron) |
| **Heinz bodies** |  | G6PD deficiency | Denatured and precipitated hemoglobin (contain iron)<br>Phagocytic removal of Heinz bodies → bite cells<br>Requires supravital stain (eg, crystal violet) to be visualized |

## Anemias

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**Reticulocyte production index**

Also called corrected reticulocyte count. Used to correct falsely elevated reticulocyte count in anemia. Measures appropriate bone marrow response to anemic conditions (effective erythropoiesis). High RPI (>3) indicates compensatory RBC production; low RPI (<2) indicates inadequate response to correct anemia. Calculated as:

$$RPI = \frac{\text{reticulocyte } \% \times \text{actual Hct}}{\text{normal Hct } (\approx 45\%)}$$

## Microcytic, hypochromic anemias

MCV < 80 fL.

### Iron deficiency

↓ iron due to chronic bleeding (eg, GI loss, menorrhagia), malnutrition, absorption disorders, GI surgery (eg, gastrectomy), or ↑ demand (eg, pregnancy) → ↓ final step in heme synthesis.

Labs: ↓ iron, ↑ TIBC, ↓ ferritin, ↑ free erythrocyte protoporphyrin, ↑ RDW, ↓ RI. Microcytosis and hypochromasia (↑ central pallor) A.

Symptoms: fatigue, conjunctival pallor B, pica (persistent craving and compulsive eating of nonfood substances), spoon nails (koilonychia).

May manifest as glossitis, cheilosis, Plummer-Vinson syndrome (triad of iron deficiency anemia, esophageal webs, and dysphagia).

### α-thalassemia

α-globin gene deletions on chromosome 16 → ↓ α-globin synthesis. May have *cis* deletion (deletions occur on same chromosome) or *trans* deletion (deletions occur on separate chromosomes). Normal is αα/αα. Often ↑ RBC count, in contrast to iron deficiency anemia.

| NUMBER OF α-GLOBIN GENES DELETED | DISEASE | CLINICAL OUTCOME |
|---|---|---|
| 1 (α α/α –) | α-thalassemia minima | No anemia (silent carrier) |
| 2 (α –/α –; *trans*) or (α α/– –; *cis*) | α-thalassemia minor | Mild microcytic, hypochromic anemia; *cis* deletion may worsen outcome for the carrier's offspring |
| 3 (– –/– α) | Hemoglobin H disease (HbH); excess β-globin forms $\beta_4$ | Moderate to severe microcytic hypochromic anemia |
| 4 (– –/– –) | Hemoglobin Barts disease; no α-globin, excess γ-globin forms $\gamma_4$ | Hydrops fetalis; incompatible with life |

### β-thalassemia

Point mutations in splice sites and promoter sequences on chromosome 11 → ↓ β-globin synthesis. ↑ prevalence in people of Mediterranean descent.

β-thalassemia minor (heterozygote): β chain is underproduced. Usually asymptomatic. Diagnosis confirmed by ↑ $HbA_2$ (> 3.5%) on electrophoresis.

β-thalassemia major (homozygote): β chain is absent → severe microcytic, hypochromic anemia with target cells and increased anisopoikilocytosis C requiring blood transfusion (2° hemochromatosis). Marrow expansion ("crew cut" on skull x-ray) → skeletal deformities (eg, "chipmunk" facies). Extramedullary hematopoiesis → hepatosplenomegaly. ↑ risk of parvovirus B19–induced aplastic crisis. ↑ HbF ($\alpha_2\gamma_2$), $HbA_2$ ($\alpha_2\delta_2$). HbF is protective in the infant and disease becomes symptomatic only after 6 months, when fetal hemoglobin declines.

HbS/β-thalassemia heterozygote: mild to moderate sickle cell disease depending on amount of β-globin production.

## Microcytic, hypochromic anemias *(continued)*

**Lead poisoning**

Lead inhibits ferrochelatase and ALA dehydratase → ↓ heme synthesis and ↑ RBC protoporphyrin. Also inhibits rRNA degradation → RBCs retain aggregates of rRNA (basophilic stippling).

Symptoms of **LEAD** poisoning:

- **L**ead **L**ines on gingivae (Burton lines) and on metaphyses of long bones D on x-ray.
- **E**ncephalopathy and **E**rythrocyte basophilic stippling.
- **A**bdominal colic and sideroblastic **A**nemia.
- **D**rops—wrist and foot drop.

Treatment: chelation with succimer, EDTA, dimercaprol.

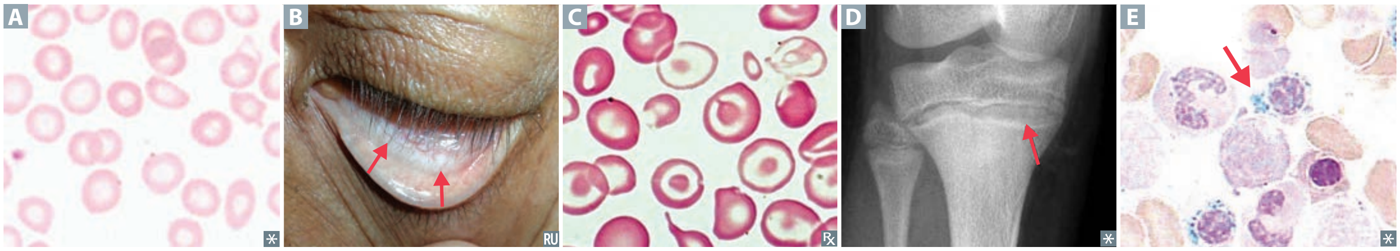
Exposure risk ↑ in old houses with chipped paint (children) and workplace (adults).

**Sideroblastic anemia**

Causes: genetic (eg, X-linked defect in ALA synthase gene), acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead poisoning, vitamin $B_6$ deficiency, copper deficiency, drugs [eg, isoniazid, linezolid]).

Lab findings: ↑ iron, normal/↓ TIBC, ↑ ferritin. Ringed sideroblasts (with iron-laden, Prussian blue–stained mitochondria) seen in bone marrow E. Peripheral blood smear: basophilic stippling of RBCs. Some acquired variants may be normocytic or macrocytic.

Treatment: pyridoxine ($B_6$, cofactor for ALA synthase).




## Interpretation of iron studies

| | Iron deficiency | Chronic disease | Hemochromatosis | Pregnancy/ OCP use |
|---|---|---|---|---|
| Serum iron | ↓ | ↓ | ↑ | — |
| Transferrin or TIBC | ↑ | ↓[a] | ↓ | ↑ |
| Ferritin | ↓ | ↑ | ↑ | — |
| % transferrin saturation (serum iron/TIBC) | ↓↓ | —/↓ | ↑↑ | ↓ |

↑↓ = 1° disturbance.

**Transfer**rin—**transport**s iron in blood.

TIBC—indirectly measures transferrin.

Ferritin—1° iron storage protein of body.

[a]Evolutionary reasoning—pathogens use circulating iron to thrive. The body has adapted a system in which iron is stored within the cells of the body and prevents pathogens from acquiring circulating iron.

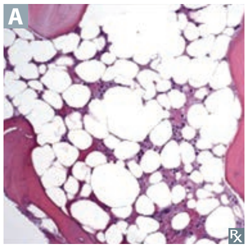
## Macrocytic anemias

MCV > 100 fL.

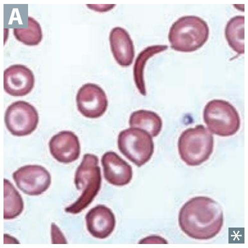
| | DESCRIPTION | FINDINGS |
|---|---|---|
| **Megaloblastic anemia** A  | Impaired DNA synthesis → maturation of nucleus of precursor cells in bone marrow delayed relative to maturation of cytoplasm.<br>Causes: vitamin $B_{12}$ deficiency, folate deficiency, medications (eg, hydroxyurea, phenytoin, methotrexate, sulfa drugs). | RBC macrocytosis, hypersegmented neutrophils (arrow in A), glossitis. |
| Folate deficiency | Causes: malnutrition (eg, chronic alcohol overuse), malabsorption, drugs (eg, methotrexate, trimethoprim, phenytoin), ↑ requirement (eg, hemolytic anemia, pregnancy). | ↑ homocysteine, normal methylmalonic acid. **No neurologic symptoms** (vs $B_{12}$ deficiency). |
| Vitamin $B_{12}$ (cobalamin) deficiency | Causes: pernicious anemia, malabsorption (eg, Crohn disease), pancreatic insufficiency, gastrectomy, insufficient intake (eg, veganism), *Diphyllobothrium latum* (fish tapeworm). | ↑ homocysteine, ↑ methylmalonic acid.<br>**Neurologic symptoms:** reversible dementia, subacute combined degeneration (due to involvement of $B_{12}$ in fatty acid pathways and myelin synthesis): spinocerebellar tract, lateral corticospinal tract, dorsal column dysfunction. Folate supplementation in vitamin $B_{12}$ deficiency can correct the anemia, but worsens neurologic symptoms.<br>Historically diagnosed with the Schilling test, a test that determines if the cause is dietary insufficiency vs malabsorption.<br>Anemia 2° to insufficient intake may take several years to develop due to liver's ability to store $B_{12}$ (vs folate deficiency, which takes weeks to months). |
| Orotic aciduria | Inability to convert orotic acid to UMP (de novo pyrimidine synthesis pathway) because of defect in UMP synthase. Autosomal recessive. Presents in children as failure to thrive, developmental delay, and megaloblastic anemia refractory to folate and $B_{12}$. No hyperammonemia (vs ornithine transcarbamylase deficiency—↑ orotic acid with hyperammonemia). | Orotic acid in urine.<br>Treatment: uridine monophosphate or uridine triacetate to bypass mutated enzyme. |
| **Nonmegaloblastic anemia** | Macrocytic anemia in which DNA synthesis is normal.<br>Causes: chronic alcohol overuse, liver disease. | RBC macrocytosis without hypersegmented neutrophils. |
| Diamond-Blackfan anemia | A congenital form of pure red cell aplasia (vs Fanconi anemia, which causes pancytopenia). Rapid-onset anemia within 1st year of life due to intrinsic defect in erythroid progenitor cells. | ↑ % HbF (but ↓ total Hb).<br>Short stature, craniofacial abnormalities, and upper extremity malformations (triphalangeal thumbs) in up to 50% of cases. |

| | |
|---|---|
| **Normocytic, normochromic anemias** | Normocytic, normochromic anemias are classified as nonhemolytic or hemolytic. The hemolytic anemias are further classified according to the cause of the hemolysis (intrinsic vs extrinsic to the RBC) and by the location of the hemolysis (intravascular vs extravascular). Hemolysis can lead to increases in LDH, reticulocytes, unconjugated bilirubin, pigmented gallstones, and urobilinogen in urine. |
| **Intravascular hemolysis** | Findings: ↓ haptoglobin, ↑ schistocytes on blood smear. Characteristic hemoglobinuria, hemosiderinuria, and urobilinogen in urine. Notable causes are mechanical hemolysis (eg, prosthetic valve), paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemias. |
| **Extravascular hemolysis** | Mechanism: macrophages in spleen clear RBCs. Findings: spherocytes in peripheral smear (most commonly due to hereditary spherocytosis and autoimmune hemolytic anemia), no hemoglobinuria/hemosiderinuria. Can present with urobilinogen in urine. |

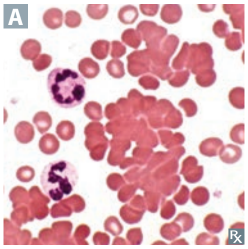
## Nonhemolytic, normocytic anemias

| | DESCRIPTION | FINDINGS |
|---|---|---|
| **Anemia of chronic disease** | Inflammation (eg, ↑ IL-6) → ↑ hepcidin (released by liver, binds ferroportin on intestinal mucosal cells and macrophages, thus inhibiting iron transport) → ↓ release of iron from macrophages and ↓ iron absorption from gut. Associated with conditions such as chronic infections, neoplastic disorders, chronic kidney disease, and autoimmune diseases (eg, SLE, rheumatoid arthritis). | ↓ iron, ↓ TIBC, ↑ ferritin.<br>Normocytic, but can become microcytic.<br>Treatment: address underlying cause of inflammation, judicious use of blood transfusion, consider erythropoiesis-stimulating agents such as EPO (eg, in chronic kidney disease). |
| **Aplastic anemia**<br> | Failure or destruction of hematopoietic stem cells. Causes (reducing volume from inside diaphysis):<br>▪ Radiation<br>▪ Viral agents (eg, EBV, HIV, hepatitis viruses)<br>▪ Fanconi anemia (autosomal recessive DNA repair defect → bone marrow failure); normocytosis or macrocytosis on CBC<br>▪ Idiopathic (immune mediated, 1° stem cell defect); may follow acute hepatitis<br>▪ Drugs (eg, benzene, chloramphenicol, alkylating agents, antimetabolites) | ↓ reticulocyte count, ↑ EPO.<br>Pancytopenia characterized by anemia, leukopenia, and thrombocytopenia (not to be confused with aplastic crisis, which causes anemia only). Normal cell morphology, but hypocellular bone marrow with fatty infiltration A (dry bone marrow tap).<br>Symptoms: fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection.<br>Treatment: withdrawal of offending agent, immunosuppressive regimens (eg, antithymocyte globulin, cyclosporine), bone marrow allograft, RBC/platelet transfusion, bone marrow stimulation (eg, GM-CSF). |

## Intrinsic hemolytic anemias

| | DESCRIPTION | FINDINGS |
|---|---|---|
| **Hereditary spherocytosis** | Primarily autosomal dominant. Due to defect in proteins interacting with RBC membrane skeleton and plasma membrane (eg, ankyrin, band 3, protein 4.2, spectrin).<br>Small, round RBCs with less surface area and no central pallor (↑ MCHC) → premature removal by spleen (extravascular hemolysis). | Splenomegaly, pigmented gallstones, aplastic crisis (parvovirus B19 infection).<br>Labs: ↓ mean fluorescence of RBCs in eosin 5-maleimide (EMA) binding test, ↑ fragility in osmotic fragility test. Normal to ↓ MCV with abundance of RBCs.<br>Treatment: splenectomy. |
| **G6PD deficiency** | X-linked recessive. G6PD defect → ↓ NADPH → ↓ reduced glutathione → ↑ RBC susceptibility to oxidative stress (eg, sulfa drugs, antimalarials, **fava beans**) → hemolysis.<br>Causes extravascular and intravascular hemolysis. | Back pain, hemoglobinuria a few days after oxidant **stress**.<br>Labs: blood smear shows RBCs with **Heinz** bodies and **bite** cells.<br>"**Stress** makes me eat **bites** of **fava beans** with **Heinz** ketchup." |
| **Pyruvate kinase deficiency** | Autosomal recessive. Pyruvate kinase defect → ↓ ATP → rigid RBCs → extravascular hemolysis. Increases levels of 2,3-BPG → ↓ hemoglobin affinity for $O_2$. | Hemolytic anemia in a newborn.<br>Labs: blood smear shows burr cells. |
| **Paroxysmal nocturnal hemoglobinuria** | Hematopoietic stem cell mutation → ↑ complement-mediated intravascular hemolysis, especially at night. Acquired *PIGA* mutation → impaired GPI anchor synthesis for decay-accelerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59), which protect RBC membrane from complement. | Triad: Coombs ⊖ hemolytic anemia, pancytopenia, venous thrombosis (eg, Budd-Chiari syndrome).<br>Pink/red urine in morning. Associated with aplastic anemia, acute leukemias.<br>Labs: CD55/59 ⊖ RBCs on flow cytometry.<br>Treatment: eculizumab (targets terminal complement protein C5). |
| **Sickle cell anemia**<br> | Point mutation in β-globin gene → single amino acid substitution (glutamic acid → valine). Mutant HbA is termed HbS. Causes extravascular and intravascular hemolysis.<br>Pathogenesis: low $O_2$, high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) → anemia, vaso-occlusive disease.<br>Newborns are initially asymptomatic because of ↑ HbF and ↓ HbS.<br>Heterozygotes (sickle cell trait) have resistance to malaria.<br>Most common autosomal recessive disease in Black population.<br>Sickle cells are crescent-shaped RBCs A.<br>"Crew cut" on skull x-ray due to marrow expansion from ↑ erythropoiesis (also seen in thalassemias). | Complications in sickle cell disease:<br>▪ Aplastic crisis (transient arrest of erythropoiesis due to parvovirus B19).<br>▪ Autosplenectomy (Howell-Jolly bodies) → ↑ risk of infection by encapsulated organisms (eg, *S pneumoniae*).<br>▪ Splenic infarct/sequestration crisis.<br>▪ *Salmonella* osteomyelitis.<br>▪ Painful vaso-occlusive crises: dactylitis (painful swelling of hands/feet), priapism, acute chest syndrome (respiratory distress, new pulmonary infiltrates on CXR, common cause of death), avascular necrosis, stroke.<br>▪ Sickling in renal medulla (↓ $Po_2$) → renal papillary necrosis → hematuria.<br>Hb electrophoresis: ↓↓ HbA, ↑ HbF, ↑↑ HbS.<br>Treatment: hydroxyurea (↑ HbF), hydration. |
| **HbC disease** | Glutamic acid–to-lycine (lysine) mutation in β-globin. Causes extravascular hemolysis. | Patients with HbSC (1 of each mutant gene) have milder disease than HbSS patients.<br>Blood smear in homozygotes: hemoglobin crystals inside RBCs, target cells. |

## Extrinsic hemolytic anemias

| | DESCRIPTION | FINDINGS |
|---|---|---|
| **Autoimmune hemolytic anemia**  | A normocytic anemia that is usually idiopathic and Coombs ⊕. Two types:<br>▪ **Warm** AIHA–chronic anemia in which primarily Ig**G** causes extravascular hemolysis. Seen in SLE and CLL and with certain drugs (eg, β-lactams, α-methyldopa). "**Warm** weather is **G**ood."<br>▪ Cold AIHA–acute anemia in which primarily Ig**M** + complement cause RBC agglutination and extravascular hemolysis upon exposure to cold → painful, blue fingers and toes. Seen in CLL, ***M**ycoplasma pneumoniae* infections, infectious **m**ononucleosis. | Spherocytes and agglutinated RBCs A on peripheral blood smear.<br>Warm AIHA treatment: steroids, rituximab, splenectomy (if refractory).<br>Cold AIHA treatment: cold avoidance, rituximab. |
| **Microangiopathic hemolytic anemia** | RBCs are damaged when passing through obstructed or narrowed vessels. Causes intravascular hemolysis.<br>Seen in DIC, TTP/HUS, SLE, HELLP syndrome, hypertensive emergency. | **Schisto**cytes (eg, "helmet cells") are seen on peripheral blood smear due to mechanical destruction (***schisto*** = to split) of RBCs. |
| **Macroangiopathic hemolytic anemia** | Prosthetic heart valves and aortic stenosis may also cause hemolytic anemia 2° to mechanical destruction of RBCs. | Schistocytes on peripheral blood smear. |
| **Hemolytic anemia due to infection** | ↑ destruction of RBCs (eg, malaria, *Babesia*). | |

## Leukopenias

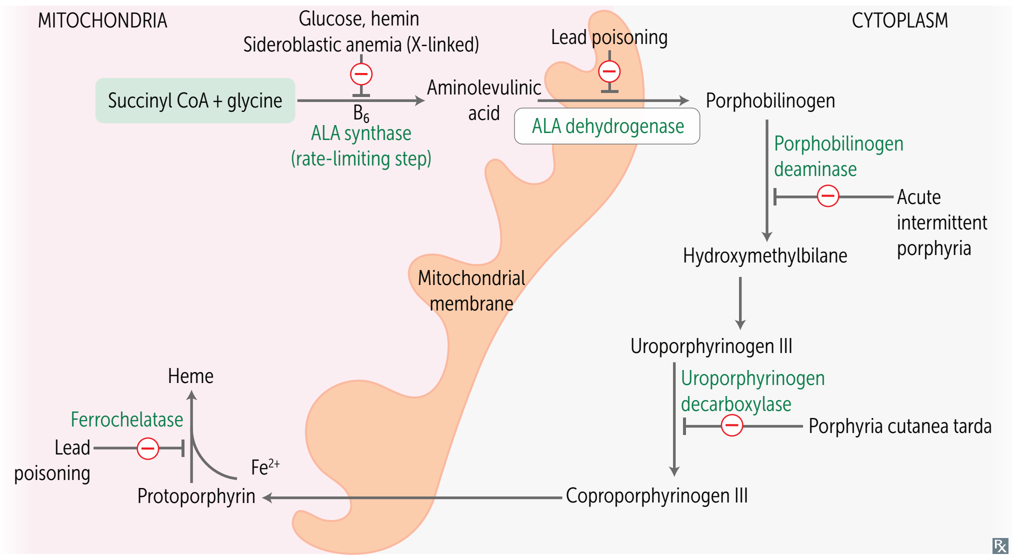
| CELL TYPE | CELL COUNT | CAUSES |
|---|---|---|
| **Neutropenia** | Absolute neutrophil count < 1500 cells/mm³<br>Severe infections typical when < 500 cells/mm³ | Sepsis/postinfection, drugs (including chemotherapy), aplastic anemia, SLE, radiation |
| **Lymphopenia** | Absolute lymphocyte count < 1500 cells/mm³ (< 3000 cells/mm³ in children) | HIV, DiGeorge syndrome, SCID, SLE, corticosteroids[a], radiation, sepsis, postoperative |
| **Eosinopenia** | Absolute eosinophil count < 30 cells/mm³ | Cushing syndrome, corticosteroids[a] |

[a]Corticosteroids cause neutrophilia, despite causing eosinopenia and lymphopenia. Corticosteroids ↓ activation of neutrophil adhesion molecules, impairing migration out of the vasculature to sites of inflammation. In contrast, corticosteroids sequester eosinophils in lymph nodes and cause apoptosis of lymphocytes.

## Heme synthesis, porphyrias, and lead poisoning

The porphyrias are hereditary or acquired conditions of defective heme synthesis that lead to the accumulation of heme precursors. Lead inhibits specific enzymes needed in heme synthesis, leading to a similar condition.

| CONDITION | AFFECTED ENZYME | ACCUMULATED SUBSTRATE | PRESENTING SYMPTOMS |
|---|---|---|---|
| **Lead poisoning**  | Ferrochelatase and ALA dehydratase | Protoporphyrin, ALA (blood) | Microcytic anemia (basophilic stippling in peripheral smear A, ringed sideroblasts in bone marrow), GI and kidney disease.<br>Children—exposure to lead paint → mental deterioration.<br>Adults—environmental exposure (eg, batteries, ammunition) → headache, memory loss, demyelination (peripheral neuropathy). |
| **Acute intermittent porphyria** | Porphobilinogen deaminase, previously called uroporphyrinogen I synthase (autosomal dominant mutation) | Porphobilinogen, ALA | Symptoms (5 P's):<br>▪ Painful abdomen<br>▪ Port wine–colored Pee<br>▪ Polyneuropathy<br>▪ Psychological disturbances<br>▪ Precipitated by factors that ↑ ALA synthase (eg, drugs [CYP450 inducers], alcohol, starvation)<br>Treatment: hemin and glucose. |
| **Porphyria cutanea tarda**  | Uroporphyrinogen decarboxylase | Uroporphyrin (tea-colored urine) | Blistering cutaneous photosensitivity and hyperpigmentation B.<br>Most common porphyria. Exacerbated with alcohol consumption.<br>Causes: familial, hepatitis C.<br>Treatment: phlebotomy, sun avoidance, antimalarials (eg, hydroxychloroquine). |



## Iron poisoning

| | Acute | Chronic |
|---|---|---|
| FINDINGS | High mortality rate associated with accidental ingestion by children (adult iron tablets may look like candy). | Seen in patients with 1° (hereditary) or 2° (eg, chronic blood transfusions for thalassemia or sickle cell disease) hemochromatosis. |
| MECHANISM | Cell death due to formation of free radicals and peroxidation of membrane lipids. | |
| SYMPTOMS/SIGNS | Abdominal pain, vomiting, GI bleeding. Radiopaque pill seen on x-ray. May progress to anion gap metabolic acidosis and multiorgan failure. Leads to scarring with GI obstruction. | Arthropathy, cirrhosis, cardiomyopathy, diabetes mellitus and skin pigmentation ("bronze diabetes"), hypogonadism. |
| TREATMENT | Chelation (eg, deferoxamine, deferasirox), gastric lavage. | Phlebotomy (patients without anemia) or chelation. |

## Coagulation disorders

PT—tests function of common and extrinsic pathway (factors I, II, V, VII, and X). Defect → ↑ **PT** (**P**lay **T**ennis **out**side [**ext**rinsic pathway]).

INR (international normalized ratio) = patient PT/control PT. 1 = normal, > 1 = prolonged. Most common test used to follow patients on warfarin, which prolongs INR.

PTT—tests function of common and **in**trinsic pathway (all factors except VII and XIII). Defect → ↑ **PTT** (**P**lay **T**able **T**ennis **in**side).

Coagulation disorders can be due to clotting factor deficiencies or acquired factor inhibitors (most commonly against factor VIII). Diagnosed with a mixing study, in which normal plasma is added to patient's plasma. Clotting factor deficiencies should correct (the PT or PTT returns to within the appropriate normal range), whereas factor inhibitors will not correct.

| DISORDER | PT | PTT | MECHANISM AND COMMENTS |
|---|---|---|---|
| **Hemophilia A, B, or C**  | — | ↑ | Intrinsic pathway coagulation defect (↑ PTT).<br>▪ **A**: deficiency of factor **VIII**; X-linked recessive. Pronounce "hemophilia **eight**."<br>▪ B: deficiency of factor IX; X-linked recessive.<br>▪ C: deficiency of factor XI; autosomal recessive.<br>Hemorrhage in hemophilia—hemarthroses (bleeding into joints, eg, knee A), easy bruising, bleeding after trauma or surgery (eg, dental procedures).<br>Treatment: desmopressin, factor VIII concentrate, emicizumab (A); factor IX concentrate (B); factor XI concentrate (C). |
| **Vitamin K deficiency** | ↑ | ↑ | General coagulation defect. Bleeding time normal.<br>↓ activity of factors II, VII, IX, X, protein C, protein S. |

## Platelet disorders

All platelet disorders have ↑ bleeding time (BT), mucous membrane bleeding, and microhemorrhages (eg, petechiae, epistaxis). Platelet count (PC) is usually low, but may be normal in qualitative disorders.

| DISORDER | PC | BT | NOTES |
|---|---|---|---|
| **Bernard-Soulier syndrome** | –/↓ | ↑ | Autosomal recessive defect in adhesion. ↓ GpIb → ↓ platelet-to-vWF adhesion.<br>Labs: abnormal ristocetin test, large platelets. |
| **Glanzmann thrombasthenia** | – | ↑ | Autosomal recessive defect in aggregation. ↓ GpIIb/IIIa (↓ integrin $\alpha_{IIb}\beta_3$) → ↓ platelet-to-platelet aggregation and defective platelet plug formation.<br>Labs: blood smear shows no platelet clumping. |
| **Immune thrombocytopenia** | ↓ | ↑ | Destruction of platelets in spleen. Anti-GpIIb/IIIa antibodies → splenic macrophages phagocytose platelets. May be idiopathic or 2° to autoimmune disorders (eg, SLE), viral illness (eg, HIV, HCV), malignancy (eg, CLL), or drug reactions.<br>Labs: ↑ megakaryocytes on bone marrow biopsy, ↓ platelet count.<br>Treatment: steroids, IVIG, rituximab, TPO receptor agonists (eg, eltrombopag, romiplostim), or splenectomy for refractory ITP. |

## Thrombotic microangiopathies

Disorders overlap significantly in symptomatology.

| | Thrombotic thrombocytopenic purpura | Hemolytic-uremic syndrome |
|---|---|---|
| EPIDEMIOLOGY | Typically females | Typically children |
| PATHOPHYSIOLOGY | Inhibition or deficiency of ADAMTS13 (a vWF metalloprotease) → ↓ degradation of vWF multimers → ↑ large vWF multimers → ↑ platelet adhesion and aggregation (microthrombi formation) | Commonly caused by Shiga toxin-producing *Escherichia coli* (STEC) infection (serotype O157:H7) |
| PRESENTATION | Triad of thrombocytopenia (↓ platelets), microangiopathic hemolytic anemia (↓ Hb, schistocytes, ↑ LDH), acute kidney injury (↑ Cr) | |
| DIFFERENTIATING SYMPTOMS | Triad + fever + neurologic symptoms | Triad + bloody diarrhea |
| LABS | Normal PT and PTT helps distinguish TTP and HUS (coagulation pathway is not activated) from DIC (coagulation pathway is activated) | |
| TREATMENT | Plasma exchange, steroids, rituximab | Supportive care |

### Mixed platelet and coagulation disorders

| DISORDER | PC | BT | PT | PTT | NOTES |
|---|---|---|---|---|---|
| **von Willebrand disease** | — | ↑ | — | —/↑ | Intrinsic pathway coagulation defect: ↓ vWF → ↑ PTT (vWF carries/protects factor VIII).<br>Defect in platelet plug formation: ↓ vWF → defect in platelet-to-vWF adhesion.<br>Most are autosomal dominant. Mild but most common inherited bleeding disorder. No platelet aggregation with ristocetin cofactor assay. Treatment: desmopressin, which releases vWF stored in endothelium. |
| **Disseminated intravascular coagulation** | ↓ | ↑ | ↑ | ↑ | Widespread clotting factor activation → deficiency in clotting factors → bleeding state (eg, blood oozing from puncture sites).<br>Causes: **S**nake bites, **S**epsis (gram ⊖), **T**rauma, **O**bstetric complications, acute **P**ancreatitis, **m**alignancy, **n**ephrotic syndrome, **t**ransfusion (**SSTOP** **m**aking **n**ew **t**hrombi).<br>Labs: schistocytes, ↑ fibrin degradation products (D-dimers), ↓ fibrinogen, ↓ factors V and VIII. |

### Hereditary thrombophilias

All autosomal dominant. Lead to hypercoagulable state.

| DISEASE | DESCRIPTION |
|---|---|
| **Antithrombin deficiency** | Has no direct effect on the PT, PTT, or thrombin time but diminishes the increase in PTT following standard heparin dosing.<br>Can also be acquired: renal failure/nephrotic syndrome → antithrombin loss in urine → ↓ inhibition of factors IIa and Xa. |
| **Factor V Leiden** | Production of mutant factor V (guanine → adenine DNA point mutation → Arg506Gln mutation near the cleavage site) that is resistant to degradation by activated protein C. Complications include DVT, cerebral vein thrombosis, recurrent pregnancy loss. |
| **Protein C or S deficiency** | ↓ ability to inactivate factors Va and VIIIa. ↑ risk of warfarin-induced skin necrosis. Together, protein **C** **C**ancels, and protein **S** **S**tops, coagulation. |
| **Prothrombin *G20210A* mutation** | Point mutation in 3′ untranslated region → ↑ production of prothrombin → ↑ plasma levels and venous clots. |

### Blood transfusion therapy

| COMPONENT | DOSAGE EFFECT | CLINICAL USE |
|---|---|---|
| **Packed RBCs** | $\uparrow$ Hb and $O_2$ carrying capacity | Acute blood loss, severe anemia |
| **Platelets** | $\uparrow$ platelet count ($\uparrow$ ~ 5000/mm$^3$/unit) | Stop significant bleeding (thrombocytopenia, qualitative platelet defects) |
| **Fresh frozen plasma/ prothrombin complex concentrate** | $\uparrow$ coagulation factor levels; FFP contains all coagulation factors and plasma proteins; PCC generally contains factors II, VII, IX, and X, as well as protein C and S | Cirrhosis, immediate anticoagulation reversal |
| **Cryoprecipitate** | Contains fibrinogen, factor VIII, factor XIII, vWF, and fibronectin | Coagulation factor deficiencies involving fibrinogen and factor VIII |

Blood transfusion risks include infection transmission (low), transfusion reactions, iron overload (may lead to 2° hemochromatosis), hypocalcemia (citrate is a $Ca^{2+}$ chelator), and hyperkalemia (RBCs may lyse in old blood units).

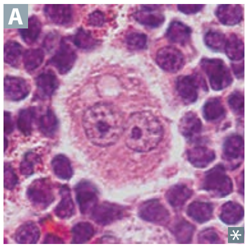
### Leukemia vs lymphoma

| | |
|---|---|
| **Leukemia** | Lymphoid or myeloid neoplasm with widespread involvement of bone marrow. Tumor cells are usually found in peripheral blood. |
| **Lymphoma** | Discrete tumor mass arising from lymph nodes. Variable clinical presentation (eg, arising in atypical sites, leukemic presentation). |

### Hodgkin vs non-Hodgkin lymphoma

| Hodgkin | Non-Hodgkin |
|---|---|
| Both may present with constitutional ("B") signs/symptoms: low-grade fever, night sweats, weight loss. | |
| Localized, single group of nodes with contiguous spread (stage is strongest predictor of prognosis). Better prognosis. | Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread. Worse prognosis. |
| Characterized by Reed-Sternberg cells. | Majority involve B cells; a few are of T-cell lineage. |
| Bimodal distribution: young adulthood and > 55 years; more common in males except for nodular sclerosing type. | Can occur in children and adults. |
| Associated with EBV. | May be associated with autoimmune diseases and viral infections (eg, HIV, EBV, HTLV). |

### Hodgkin lymphoma

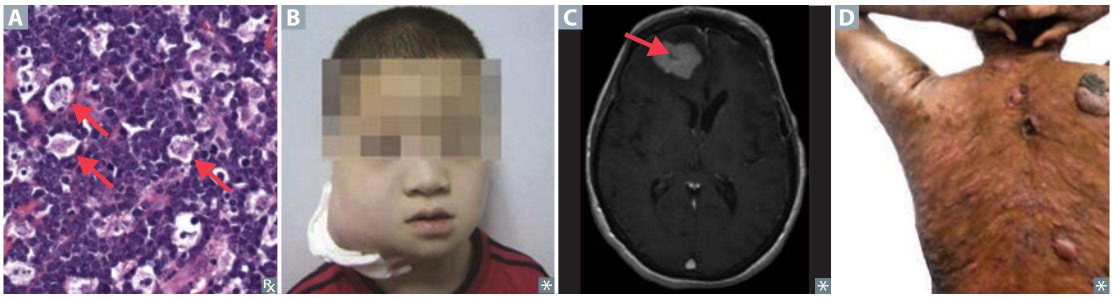


Contains Reed-Sternberg cells: distinctive tumor giant cells; binucleate or bilobed with the 2 halves as mirror images ("owl eyes" A). RS cells are CD15+ and CD30+ B-cell origin. 2 owl eyes × 15 = 30.

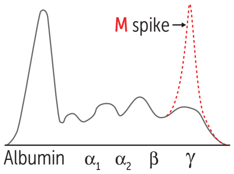
| SUBTYPE | NOTES |
|---|---|
| Nodular sclerosis | Most common |
| Lymphocyte rich | Best prognosis (the rich have better bank accounts) |
| Mixed cellularity | Eosinophilia; seen in immunocompromised patients |
| Lymphocyte depleted | Worst prognosis (the poor have worse bank accounts); seen in immunocompromised patients |

### Non-Hodgkin lymphoma

| TYPE | OCCURS IN | GENETICS | COMMENTS |
|---|---|---|---|
| **Neoplasms of mature B cells** | | | |
| **Burkitt lymphoma** | Adolescents or young adults | t(8;14)—translocation of c-*myc* (8) and heavy-chain Ig (14) | "Starry sky" appearance, sheets of lymphocytes with interspersed "tingible body" macrophages (arrows in A). Associated with EBV.<br>Jaw lesion B in endemic form in Africa; pelvis or abdomen in sporadic form. |
| **Diffuse large B-cell lymphoma** | Usually older adults, but 20% in children | Mutations in *BCL-2*, *BCL-6* | Most common type of non-Hodgkin lymphoma in adults. |
| **Follicular lymphoma** | Adults | t(14;18)—translocation of heavy-chain Ig (14) and *BCL-2* (18) | Indolent course with painless "waxing and waning" lymphadenopathy. Bcl-2 normally inhibits apoptosis. |
| **Mantle cell lymphoma** | Adult males >> adult females | t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14), CD5+ | Very aggressive, patients typically present with late-stage disease. |
| **Marginal zone lymphoma** | Adults | t(11;18) | Associated with chronic inflammation (eg, Sjögren syndrome, chronic gastritis [MALT lymphoma; may regress with *H pylori* eradication]). |
| **Primary central nervous system lymphoma** | Adults | EBV related; associated with HIV/AIDS | Considered an AIDS-defining illness. Variable presentation: confusion, memory loss, seizures. CNS mass (often single, ring-enhancing lesion on MRI) in immunocompromised patients C, needs to be distinguished from toxoplasmosis via CSF analysis or other lab tests. |
| **Neoplasms of mature T cells** | | | |
| **Adult T-cell lymphoma** | Adults | Caused by HTLV (associated with IV drug use) | Adults present with cutaneous lesions; common in Japan (T-cell in Tokyo), West Africa, and the Caribbean.<br>Lytic bone lesions, hypercalcemia. |
| **Mycosis fungoides/ Sézary syndrome** | Adults | | Mycosis fungoides: skin patches and plaques D (cutaneous T-cell lymphoma), characterized by atypical CD4+ cells with "cerebriform" nuclei and intraepidermal neoplastic cell aggregates (Pautrier microabscess). May progress to Sézary syndrome (T-cell leukemia). |



## Plasma cell dyscrasias




Characterized by monoclonal immunoglobulin (paraprotein) overproduction due to plasma cell disorder.

Labs: serum protein electrophoresis (SPEP) or free light chain (FLC) assay for initial tests (M spike on SPEP represents overproduction of a monoclonal Ig fragment). For urinalysis, use 24-hr urine protein electrophoresis (UPEP) to detect light chain, as routine urine dipstick detects only albumin.

Confirm with bone marrow biopsy.

## Multiple myeloma

Overproduction of IgG (55% of cases) > IgA.

Clinical features: **CRAB**

- Hyper**C**alcemia
- **R**enal involvement
- **A**nemia
- **B**one lytic lesions ("punched out" on X-ray **A**) → back pain.

Peripheral blood smear shows rouleaux formation **B** (RBCs stacked like poker chips).

Urinalysis shows Ig light chains (Bence Jones proteinuria) with ⊖ urine dipstick.

Bone marrow analysis shows > 10% monoclonal plasma cells with clock-face chromatin **C** and intracytoplasmic inclusions containing IgG.

Complications: ↑ infection risk, 1° amyloidosis (AL).

## Waldenstrom macroglobulinemia

Overproduction of Ig**M** (**macro**globulinemia because Ig**M** is the **largest** Ig).

Clinical features:

- Peripheral neuropathy
- No CRAB findings
- Hyperviscosity syndrome:
  - Headache
  - Blurry vision
  - Raynaud phenomenon
  - Retinal hemorrhages

Bone marrow analysis shows >10% small lymphocytes with intranuclear pseudoinclusions containing IgM (lymphoplasmacytic lymphoma).

Complication: thrombosis.

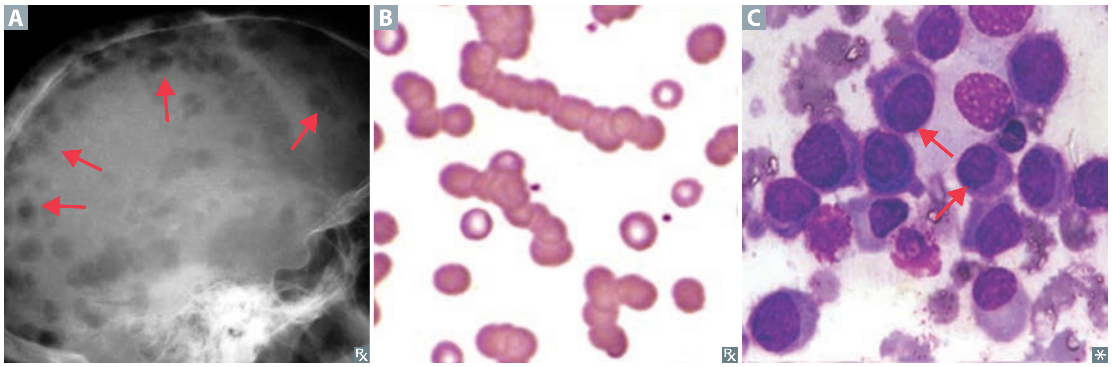
## Monoclonal gammopathy of undetermined significance

Overproduction of any Ig type.

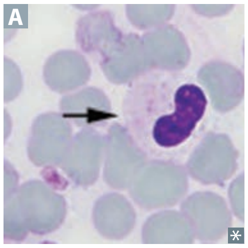
Usually asymptomatic. No CRAB findings.

Bone marrow analysis shows < 10% monoclonal plasma cells.

Complication: 1-2% risk per year of transitioning to multiple myeloma.



**Myelodysplastic syndromes**




Stem cell disorders involving ineffective hematopoiesis → defects in cell maturation of nonlymphoid lineages. Bone marrow blasts <20% (vs >20% in AML). Caused by de novo mutations or environmental exposure (eg, radiation, benzene, chemotherapy). Risk of transformation to AML.

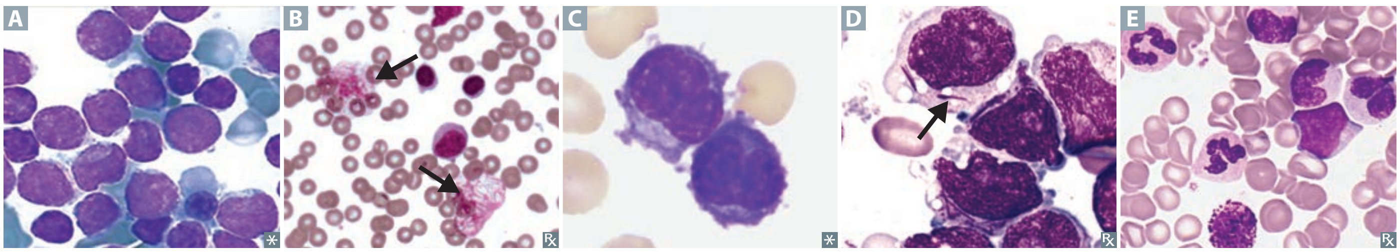
Pseudo-Pelger-Huët anomaly—neutrophils with bilobed ("duet") nuclei A. Associated with myelodysplastic syndromes or drugs (eg, immunosuppressants).

**Leukemias**

Unregulated growth and differentiation of WBCs in bone marrow → marrow failure → anemia (↓ RBCs), infections (↓ mature WBCs), and hemorrhage (↓ platelets). Usually presents with ↑ circulating WBCs (malignant leukocytes in blood), although some cases present with normal/↓ WBCs.

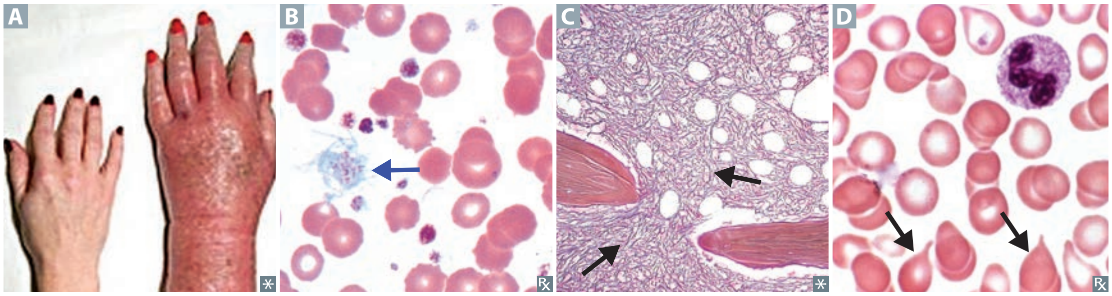
Leukemic cell infiltration of liver, spleen, lymph nodes, and skin (leukemia cutis) possible.

| TYPE | NOTES |
|---|---|
| **Lymphoid neoplasms** | |
| **Acute lymphoblastic leukemia/lymphoma** | Most frequently occurs in children; less common in adults (worse prognosis). T-cell ALL can present as mediastinal mass (presenting as SVC-like syndrome). Associated with Down syndrome.<br>Peripheral blood and bone marrow have ↑↑↑ lymphoblasts A.<br>TdT+ (marker of pre-T and pre-B cells), CD10+ (marker of pre-B cells).<br>Most responsive to therapy.<br>May spread to CNS and testes.<br>t(12;21) → better prognosis; t(9;22) (Philadelphia chromosome) → worse prognosis. |
| **Chronic lymphocytic leukemia/small lymphocytic lymphoma** | Age > 60 years. Most common adult leukemia. CD20+, CD23+, CD5+ B-cell neoplasm. Often asymptomatic, progresses slowly; smudge cells B in peripheral blood smear; autoimmune hemolytic anemia. **CLL** = **C**rushed **L**ittle **L**ymphocytes (smudge cells).<br>Richter transformation—CLL/SLL transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL). |
| **Hairy cell leukemia** | Adult males. Mature B-cell tumor. Cells have filamentous, hair-like projections (fuzzy appearing on LM C). Peripheral lymphadenopathy is uncommon.<br>Causes marrow fibrosis → dry tap on aspiration. Patients usually present with massive splenomegaly and pancytopenia.<br>Stains **TRAP** (**T**artrate-**R**esistant **A**cid **P**hosphatase) ⊕ (**TRAP**ped in a **hairy** situation). TRAP stain largely replaced with flow cytometry. Associated with *BRAF* mutations.<br>Treatment: purine analogs (cladribine, pentostatin). |
| **Myeloid neoplasms** | |
| **Acute myelogenous leukemia** | Median onset 65 years. Auer rods D; myeloperoxidase ⊕ cytoplasmic inclusions seen mostly in APL (formerly M3 AML); ↑↑↑ circulating myeloblasts on peripheral smear.<br>Risk factors: prior exposure to alkylating chemotherapy, radiation, myeloproliferative disorders, Down syndrome (typically acute megakaryoblastic leukemia [formerly M7 AML]). APL: t(15;17), responds to all-*trans* retinoic acid (vitamin A) and arsenic trioxide, which induce differentiation of promyelocytes; DIC is a common presentation. |
| **Chronic myelogenous leukemia** | Peak incidence: 45—85 years; median age: 64 years. Defined by the Philadelphia chromosome (t[9;22], *BCR-ABL*) and myeloid stem cell proliferation. Presents with dysregulated production of mature and maturing granulocytes (eg, neutrophils, metamyelocytes, myelocytes, basophils E) and splenomegaly. May accelerate and transform to AML or ALL ("blast crisis").<br>Responds to BCR-ABL tyrosine kinase inhibitors (eg, imatinib). |



| | |
|---|---|
| **Myeloproliferative neoplasms** | Malignant hematopoietic neoplasms with varying impacts on WBCs and myeloid cell lines. |
| **Polycythemia vera** | Primary polycythemia. Disorder of ↑ RBCs, usually due to acquired *JAK2* mutation. May present as intense itching after shower (aquagenic pruritus). Rare but classic symptom is erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities A.<br>↓ EPO (vs 2° polycythemia, which presents with endogenous or artificially ↑ EPO).<br>Treatment: phlebotomy, hydroxyurea, ruxolitinib (JAK1/2 inhibitor). |
| **Essential thrombocythemia** | Characterized by massive proliferation of megakaryocytes and platelets. Symptoms include bleeding and thrombosis. Blood smear shows markedly increased number of platelets, which may be large or otherwise abnormally formed B. Erythromelalgia may occur. |
| **Myelofibrosis** | Atypical megakaryocyte hyperplasia → ↑ TGF-β secretion → ↑ fibroblast activity → obliteration of bone marrow with fibrosis C. Associated with massive splenomegaly and "teardrop" RBCs D.<br>"Bone marrow cries because it's fibrosed and is a dry tap." |

| | RBCs | WBCs | PLATELETS | PHILADELPHIA CHROMOSOME | *JAK2* MUTATIONS |
|---|---|---|---|---|---|
| Polycythemia vera | ↑ | ↑ | ↑ | ⊖ | ⊕ |
| Essential thrombocythemia | – | – | ↑ | ⊖ | ⊕ (30–50%) |
| Myelofibrosis | ↓ | Variable | Variable | ⊖ | ⊕ (30–50%) |
| CML | ↓ | ↑ | ↑ | ⊕ | ⊖ |




## Leukemoid reaction vs chronic myelogenous leukemia

| | Leukemoid reaction | Chronic myelogenous leukemia |
|---|---|---|
| DEFINITION | Reactive neutrophilia >50,000 cells/mm$^3$ | Myeloproliferative neoplasm ⊕ for *BCR-ABL* |
| NEUTROPHIL MORPHOLOGY | Toxic granulation, Döhle bodies, cytoplasmic vacuoles | Pseudo-Pelger-Huët anomaly |
| LAP SCORE | ↑ | ↓ (LAP enzyme ↓ in malignant neutrophils) |
| EOSINOPHILS AND BASOPHILS | Normal | ↑ |

## Polycythemia

| | PLASMA VOLUME | RBC MASS | $O_2$ SATURATION | EPO LEVELS | ASSOCIATIONS |
|---|---|---|---|---|---|
| Relative | ↓ | — | — | — | Dehydration, burns. |
| Appropriate absolute | — | ↑ | ↓ | ↑ | Lung disease, congenital heart disease, high altitude. |
| Inappropriate absolute | — | ↑ | — | ↑ | Exogenous EPO: athlete abuse ("blood doping"). Inappropriate EPO secretion: malignancy (eg, RCC, HCC). |
| Polycythemia vera | ↑ | ↑↑ | — | ↓ | EPO ↓ in PCV due to negative feedback suppressing renal EPO production. |

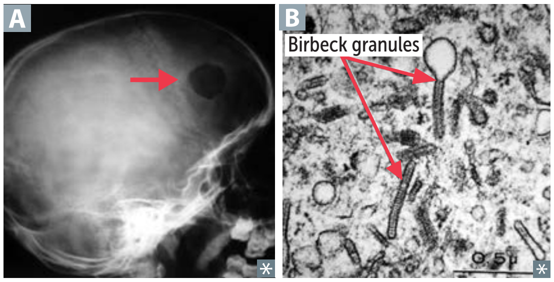
↑↓ = 1° disturbance

## Chromosomal translocations

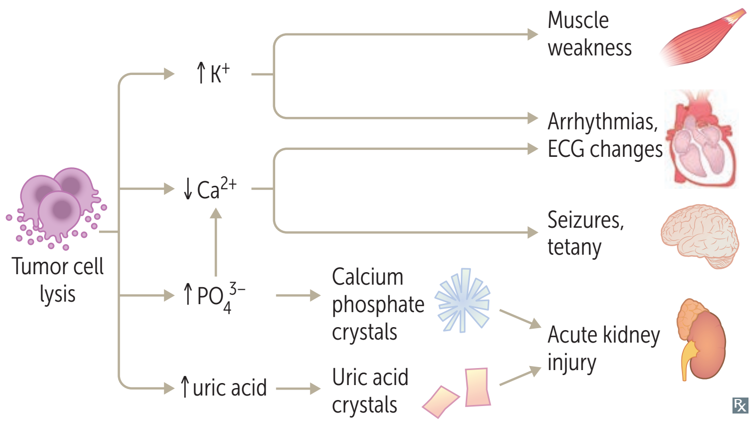
| TRANSLOCATION | ASSOCIATED DISORDER | NOTES |
|---|---|---|
| t(8;14) | Burkitt (Burk-8) lymphoma (c-*myc* activation) | The Ig heavy chain genes on chromosome 14 are constitutively expressed. When other genes (eg, *c-myc* and *BCL-2*) are translocated next to this heavy chain gene region, they are overexpressed. |
| t(11;14) | Mantle cell lymphoma (cyclin D1 activation) | |
| t(11;18) | Marginal zone lymphoma | |
| t(14;18) | Follicular lymphoma (*BCL*-2 activation) | |
| t(15;17) | APL (formerly M3 type of AML) | |
| t(9;22) (**Philadelphia** chromosome) | **CML** (*BCR-ABL* hybrid), ALL (less common); **Philadelphia CreaML** cheese | |

## Langerhans cell histiocytosis

Collective group of proliferative disorders of Langerhans cells. Presents in a child as lytic bone lesions A and skin rash or as recurrent otitis media with a mass involving the mastoid bone. Cells are functionally immature and do not effectively stimulate primary T cells via antigen presentation. Cells express S-100 (mesodermal origin) and CD1a. Birbeck granules ("tennis rackets" or rod shaped on EM) are characteristic B.

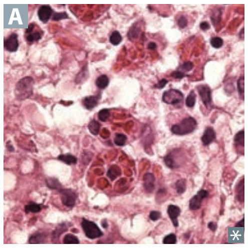


### Tumor lysis syndrome




Oncologic emergency triggered by massive tumor cell lysis, seen most often with lymphomas/leukemias. Usually caused by treatment initiation, but can occur spontaneously with fast-growing cancers. Release of $K^+$ → hyperkalemia, release of $PO_4^{3-}$ → hyperphosphatemia, hypocalcemia due to $Ca^{2+}$ sequestration by $PO_4^{3-}$. ↑ nucleic acid breakdown → hyperuricemia → acute kidney injury. Prevention and treatment include aggressive hydration, allopurinol, rasburicase.

### Hemophagocytic lymphohistiocytosis




Systemic overactivation of macrophages and cytotoxic T cells → fever, pancytopenia, hepatosplenomegaly, ↑↑ serum ferritin levels. Can be inherited or 2° to strong immunologic activation (eg, after EBV infection, malignancy). Bone marrow biopsy shows macrophages phagocytosing marrow elements A.

## ▶ HEMATOLOGY AND ONCOLOGY—PHARMACOLOGY

### Heparin

| | |
|---|---|
| MECHANISM | Activates antithrombin, which ↓ action primarily of factors IIa (thrombin) and Xa. Short half-life. |
| CLINICAL USE | Immediate anticoagulation for pulmonary embolism (PE), acute coronary syndrome, MI, deep venous thrombosis (DVT). Used during pregnancy (does not cross placenta). Monitor PTT. |
| ADVERSE EFFECTS | Bleeding (reverse with protamine sulfate), heparin-induced thrombocytopenia (HIT), osteoporosis (with long-term use), drug-drug interactions.<br>▪ HIT type 1—mild (platelets >100,000/mm$^3$), transient, nonimmunologic drop in platelet count that typically occurs within the first 2 days of heparin administration. Not clinically significant.<br>▪ HIT type 2—development of IgG antibodies against heparin-bound platelet factor 4 (PF4) that typically occurs 5–10 days after heparin administration. Antibody-heparin-PF4 complex binds and activates platelets → removal by splenic macrophages and thrombosis →↓↓ platelet count. Highest risk with unfractionated heparin. |
| NOTES | Low-molecular-weight heparins (eg, enoxaparin, dalteparin) act mainly on factor Xa. Fondaparinux acts only on factor Xa. Have better bioavailability and 2–4× longer half life than unfractionated heparin; can be administered subcutaneously and without lab monitoring. LMWHs undergo renal clearance (vs hepatic clearance of unfractionated heparin) and must be used with caution in patients with renal insufficiency. Not easily reversible. |

## Warfarin

| | |
|---|---|
| MECHANISM | Inhibits vitamin K epoxide reductase by competing with vitamin K → inhibition of vitamin K–dependent γ-carboxylation of clotting factors II, VII, IX, and X and proteins C and S. Metabolism affected by polymorphisms in the gene for vitamin K epoxide reductase complex (*VKORC1*). In laboratory assay, has effect on **ex**trinsic pathway and ↑ **PT**. Long half-life.<br>"The **ex**-**P**residen**T** went to **war**(farin)." |
| CLINICAL USE | Chronic anticoagulation (eg, venous thromboembolism prophylaxis and prevention of stroke in atrial fibrillation). Not used in pregnant patients (because warfarin, unlike heparin, crosses placenta). Monitor PT/INR. |
| ADVERSE EFFECTS<br> | Bleeding, teratogenic effects, skin/tissue necrosis A, drug-drug interactions (metabolized by cytochrome P-450 [CYP2C9]).<br>Initial risk of hypercoagulation: protein C has shorter half-life than factors II and X. Existing protein C depletes before existing factors II and X deplete, and before warfarin can reduce factors II and X production → hypercoagulation. Skin/tissue necrosis within first few days of large doses believed to be due to small vessel microthrombosis.<br>Heparin "bridging": heparin frequently used when starting warfarin. Heparin's activation of antithrombin enables anticoagulation during initial, transient hypercoagulable state caused by warfarin. Initial heparin therapy reduces risk of recurrent venous thromboembolism and skin/tissue necrosis.<br>For reversal of warfarin, give vitamin K. For rapid reversal, give FFP or PCC. |

## Heparin vs warfarin

| | Heparin | Warfarin |
|---|---|---|
| ROUTE OF ADMINISTRATION | Parenteral (IV, SC) | Oral |
| SITE OF ACTION | Blood | Liver |
| ONSET OF ACTION | Rapid (seconds) | Slow, limited by half-lives of normal clotting factors |
| DURATION OF ACTION | Hours | Days |
| MONITORING | PTT (intrinsic pathway) | PT/INR (extrinsic pathway) |
| CROSSES PLACENTA | No | Yes (teratogenic) |

## Direct coagulation factor inhibitors

| DRUG | MECHANISM | CLINICAL USE | ADVERSE EFFECTS |
|---|---|---|---|
| **Bivalirudin, argatroban, dabigatran** | Directly inhibit thrombin (factor IIa) | Venous thromboembolism, atrial fibrillation. Can be used in HIT, when heparin is **BAD** for the patient | Bleeding (reverse dabigatran with idarucizumab)<br>Dabigatran is the only oral agent in class<br>Do not require lab monitoring |
| **Apixaban, edoxaban, rivaroxaban** | Directly inhibit factor **Xa** | Treatment and prophylaxis for DVT and PE; stroke prophylaxis in patients with atrial fibrillation | Bleeding (reverse with ande**xa**net alfa)<br>Oral agents that do not usually require lab monitoring |

## Anticoagulation reversal

| ANTICOAGULANT | REVERSAL AGENT | NOTES |
|---|---|---|
| **Heparin** | Protamine sulfate | ⊕ charged peptide that binds ⊖ charged heparin |
| **Warfarin** | Vitamin K (slow) +/– FFP or PCC (rapid) | |
| **Dabigatran** | Idarucizumab | Monoclonal antibody Fab fragments |
| **Direct factor Xa inhibitors** | Andexanet alfa | Recombinant modified factor Xa (inactive) |

## Antiplatelets

All work by ↓ platelet aggregation.

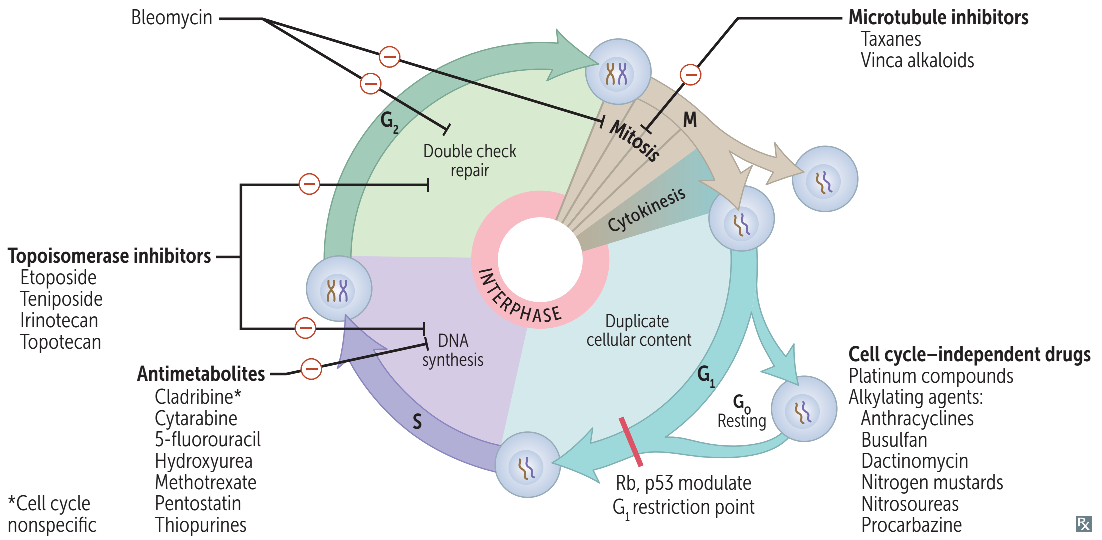
| DRUG | MECHANISM | CLINICAL USE | ADVERSE EFFECTS |
|---|---|---|---|
| **Aspirin** | Irreversibly blocks COX → ↓ $TXA_2$ release | Acute coronary syndrome; coronary stenting. ↓ incidence or recurrence of thrombotic stroke | Gastric ulcers, tinnitus, allergic reactions, renal injury |
| **Clopidogrel, prasugrel, ticagrelor, ticlopidine** | Block ADP ($P2Y_{12}$) receptor → ↓ ADP-induced expression of GpIIb/IIIa | Same as aspirin; dual antiplatelet therapy | Neutropenia (ticlopidine); TTP may be seen |
| **Abciximab, eptifibatide, tirofiban** | Block GpIIb/IIIa (fibrinogen receptor) on activated platelets. Abciximab is made from monoclonal antibody Fab fragments | Unstable angina, percutaneous coronary intervention | Bleeding, thrombocytopenia |
| **Cilostazol, dipyridamole** | Block phosphodiesterase → ↓ cAMP in platelets | Intermittent claudication, stroke prevention, cardiac stress testing, prevention of coronary stent restenosis | Nausea, headache, facial flushing, hypotension, abdominal pain |

## Thrombolytics

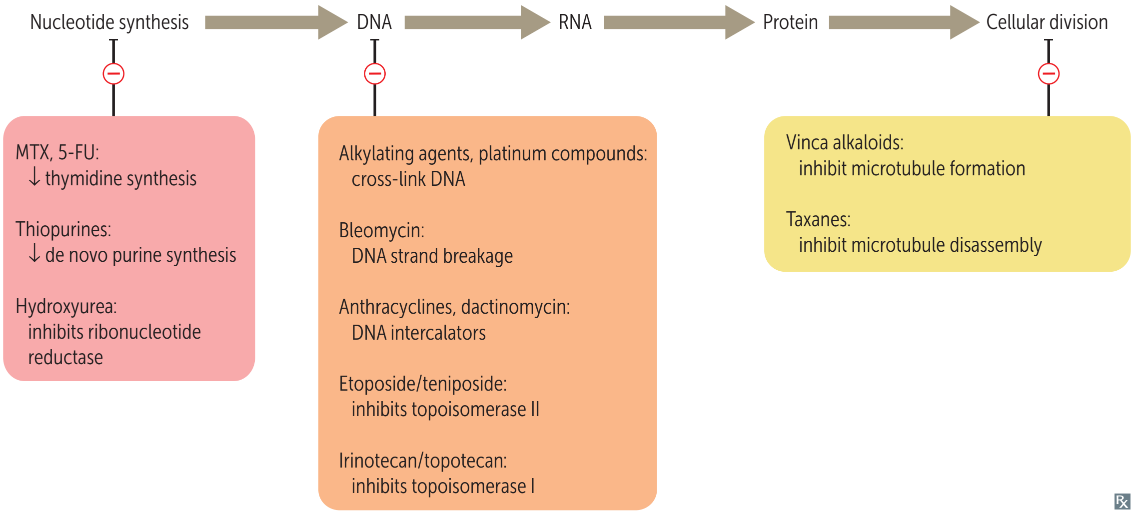
Alteplase (tPA), reteplase (rPA), streptokinase, tenecteplase (TNK-tPA).

| | |
|---|---|
| MECHANISM | Directly or indirectly aid conversion of plasminogen to plasmin, which cleaves thrombin and fibrin clots. ↑ PT, ↑ PTT, no change in platelet count. |
| CLINICAL USE | Early MI, early ischemic stroke, direct thrombolysis of severe PE. |
| ADVERSE EFFECTS | Bleeding. Contraindicated in patients with active bleeding, history of intracranial bleeding, recent surgery, known bleeding diatheses, or severe hypertension. Nonspecific reversal with antifibrinolytics (eg, aminocaproic acid, tranexamic acid), platelet transfusions, and factor corrections (eg, cryoprecipitate, FFP, PCC). |

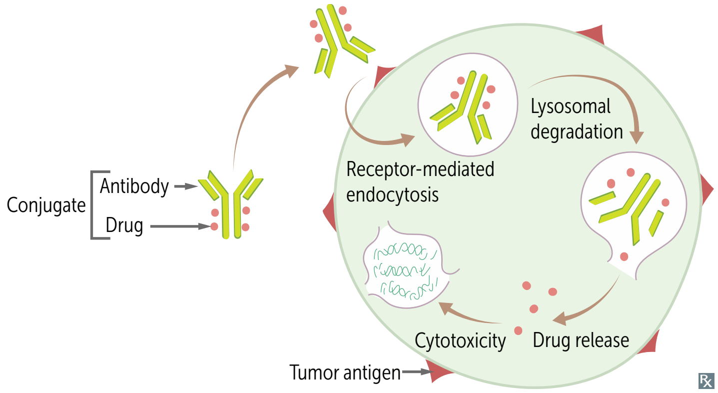
## Cancer therapy—cell cycle




## Cancer therapy—targets



### Antibody-drug conjugates




Formed by linking monoclonal antibodies with cytotoxic chemotherapeutic drugs. Antibody selectivity against tumor antigens allows targeted drug delivery to tumor cells while sparing healthy cells → ↑ efficacy and ↓ toxicity.

Example: ado-trastuzumab emtansine (T-DM1) for HER2 ⊕ breast cancer.

### Antitumor antibiotics

All are cell cycle nonspecific, except bleomycin which is $G_2$/M phase specific.

| DRUG | MECHANISM | CLINICAL USE | ADVERSE EFFECTS |
|---|---|---|---|
| **Bleomycin** | Induces free radical formation → breaks in DNA strands | Testicular cancer, Hodgkin lymphoma | Pulmonary fibrosis, skin hyperpigmentation |
| **Dactinomycin (actinomycin D)** | Intercalates into DNA, preventing RNA synthesis | Wilms tumor, Ewing sarcoma, rhabdomyosarcoma | Myelosuppression |
| **Anthracyclines** Doxorubicin, daunorubicin | Generate free radicals<br>Intercalate in DNA → breaks in DNA → ↓ replication<br>Inhibit topoisomerase II | Solid tumors, leukemias, lymphomas | Dilated cardiomyopathy (often irreversible; prevent with dexrazoxane), myelosuppression, alopecia |

**Antimetabolites** All are S-phase specific except cladribine, which is cell cycle nonspecific.

| DRUG | MECHANISM | CLINICAL USE | ADVERSE EFFECTS |
|---|---|---|---|
| **Thiopurines** Azathioprine, 6-mercaptopurine | Purine (thiol) analogs → ↓ de novo purine synthesis<br>AZA is converted to 6-MP, which is then activated by HGPRT | Rheumatoid arthritis, IBD, SLE, ALL; steroid-refractory disease<br>Prevention of organ rejection<br>Weaning from steroids | Myelosuppression; GI, liver toxicity<br>6-MP is inactivated by xanthine oxidase (↑ toxicity with allopurinol or febuxostat) |
| **Cladribine, pentostatin** | Purine analogs → multiple mechanisms (eg, inhibition of ADA, DNA strand breaks) | Hairy cell leukemia | Myelosuppression |
| **Cytarabine (arabinofuranosyl cytidine)** | Pyrimidine analog → DNA chain termination<br>Inhibits DNA polymerase | Leukemias (AML), lymphomas | Myelosuppression |
| **5-Fluorouracil** | Pyrimidine analog bioactivated to 5-FdUMP → thymidylate synthase inhibition → ↓ dTMP → ↓ DNA synthesis<br>Capecitabine is a prodrug | Colon cancer, pancreatic cancer, actinic keratosis, basal cell carcinoma (topical)<br>Effects enhanced with the addition of leucovorin | Myelosuppression, palmar-plantar erythrodysesthesia (hand-foot syndrome) |
| **Hydroxyurea** | Inhibits ribonucleotide reductase → ↓ DNA synthesis | Myeloproliferative disorders (eg, CML, polycythemia vera), sickle cell disease (↑ HbF) | Severe myelosuppression, megaloblastic anemia |
| **Methotrexate** | Folic acid analog that competitively inhibits dihydrofolate reductase → ↓ dTMP → ↓ DNA synthesis | Cancers: leukemias (ALL), lymphomas, choriocarcinoma, sarcomas<br>Nonneoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis | Myelosuppression (reversible with leucovorin "rescue"), hepatotoxicity, mucositis (eg, mouth ulcers), pulmonary fibrosis, folate deficiency (teratogenic), nephrotoxicity |

**Alkylating agents** All are cell cycle nonspecific.

| DRUG | MECHANISM | CLINICAL USE | ADVERSE EFFECTS |
|---|---|---|---|
| **Busulfan** | Cross-links DNA | Used to ablate patient's bone marrow before bone marrow transplantation | Severe myelosuppression (in almost all cases), pulmonary fibrosis, hyperpigmentation |
| **Nitrogen mustards**<br>Cyclophosphamide, ifosfamide | Cross-link DNA<br>Require bioactivation by liver | Solid tumors, leukemia, lymphomas, rheumatic disease (eg, SLE, granulomatosis with polyangiitis) | Myelosuppression, SIADH, Fanconi syndrome (ifosfamide), hemorrhagic cystitis and bladder cancer (prevent with mesna) |
| **Nitrosoureas**<br>Carmustine, lomustine | Cross-link DNA<br>Require bioactivation<br>Cross blood-brain barrier → CNS entry | Brain tumors (including **glio**blastoma multiforme)<br>Put **nitro** in your **Mus**tang and travel the **globe** | CNS toxicity (convulsions, dizziness, ataxia) |
| **Procarbazine** | Mechanism unknown<br>Weak MAO inhibitor | Hodgkin lymphoma, brain tumors | Bone marrow suppression, pulmonary toxicity, leukemia, disulfiram-like reaction |

**Platinum compounds** Cisplatin, carboplatin, oxaliplatin.

| | |
|---|---|
| MECHANISM | Cross-link DNA. Cell cycle nonspecific. |
| CLINICAL USE | Solid tumors (eg, testicular, bladder, ovarian, GI, lung), lymphomas. |
| ADVERSE EFFECTS | Nephrotoxicity (eg, Fanconi syndrome; prevent with amifostine), peripheral neuropathy, ototoxicity. |

**Microtubule inhibitors** All are M-phase specific.

| DRUG | MECHANISM | CLINICAL USE | ADVERSE EFFECTS |
|---|---|---|---|
| **Taxanes**<br>Docetaxel, paclitaxel | Hyper**stabilize** polymerized microtubules → prevent mitotic spindle breakdown | Various tumors (eg, ovarian and breast carcinomas) | Myelosuppression, neuropathy, hypersensitivity<br>**Tax**es **stabilize** society |
| **Vinca alkaloids**<br>Vincristine, vinblastine | Bind β-tubulin and inhibit its polymerization into microtubules → prevent mitotic spindle formation | Solid tumors, leukemias, Hodgkin and non-Hodgkin lymphomas | Vin**cris**tine (**cris**ps the nerves): neurotoxicity (axonal neuropathy), constipation (including ileus)<br>Vin**blast**ine (**blast**s the marrow): myelosuppression |

## Topoisomerase inhibitors

All cause ↑ DNA degradation resulting in cell cycle arrest in S and $G_2$ phases.

| DRUG | MECHANISM | CLINICAL USE | ADVERSE EFFECTS |
|---|---|---|---|
| **Irinotecan, topotecan** | Inhibit topoisomerase **I** "-tec**one**" | Colon, ovarian, small cell lung cancer | Severe myelosuppression, diarrhea |
| **Etoposide, teniposide** | Inhibit topoisomerase **II** "-**both**side" | Testicular, small cell lung cancer, leukemia, lymphoma | Myelosuppression, alopecia |

## Tamoxifen

| | |
|---|---|
| MECHANISM | Selective estrogen receptor modulator with complex mode of action: antagonist in breast tissue, partial agonist in endometrium and bone. Blocks the binding of estrogen to ER in ER ⊕ cells. |
| CLINICAL USE | Prevention and treatment of breast cancer, prevention of gynecomastia in patients undergoing prostate cancer therapy. |
| ADVERSE EFFECTS | Hot flashes, ↑ risk of thromboembolic events (eg, DVT, PE) and endometrial cancer. |

## Anticancer monoclonal antibodies

Work against extracellular targets to neutralize them or to promote immune system recognition (eg, ADCC by NK cells).

| AGENT | TARGET | CLINICAL USE | ADVERSE EFFECTS |
|---|---|---|---|
| **Alemtuzumab** | CD52 | Chronic **lym**phocytic leukemia (CLL), multiple sclerosis. | ↑ risk of infections and autoimmunity (eg, ITP) |
| **Bevacizumab** | VEGF (inhibits **b**lood **v**essel formation) | Colorectal cancer (CRC), renal cell carcinoma (RCC), non–small cell lung cancer (NSCLC), angioproliferative retinopathy | Hemorrhage, blood clots, impaired wound healing |
| **Cetuximab, panitumumab** | EGFR | Metastatic CRC (wild-type RAS), head and neck cancer | Rash, elevated LFTs, diarrhea |
| **Rituximab** | CD20 | Non-Hodgkin lymphoma, CLL, rheumatoid arthritis, ITP, TTP, AIHA, multiple sclerosis | ↑ risk of PML in patients with JC virus |
| **Trastuzumab** | **HER**2 ("**trust HER**") | Breast cancer, gastric cancer | Dilated **cardiomyopathy** (often reversible). "**Heart**ceptin" |
| **Pembrolizumab, nivolumab, cemiplimab** | PD-1 | Various tumors (eg, NSCLC, RCC, melanoma, urothelial carcinoma) | ↑ risk of autoimmunity (eg, dermatitis, enterocolitis, hepatitis, pneumonitis, endocrinopathies) |
| **Atezolizumab, durvalumab, avelumab** | PD-L1 | | |
| **Ipilimumab** | CTLA-4 | | |

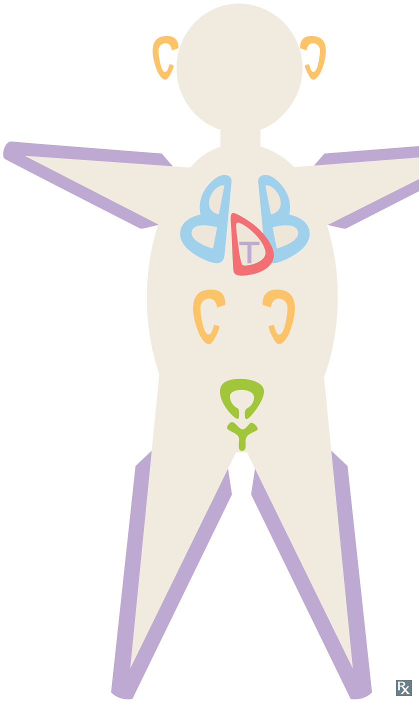
### Anticancer small molecule inhibitors

| AGENT | TARGET | CLINICAL USE | ADVERSE EFFECTS |
|---|---|---|---|
| **Alectinib** | ALK | Non–small cell lung cancer | Edema, rash, diarrhea |
| **Erlotinib, gefitinib, afatinib** | EGFR | Non–small cell lung cancer | Rash, diarrhea |
| **Imatinib, dasatinib, nilotinib** | BCR-ABL (also other tyrosine kinases [eg, c-KIT]) | CML, ALL, GISTs | Myelosuppression, ↑ LFTs, edema, myalgias |
| **Ruxolitinib** | JAK1/2 | Polycythemia vera | Bruises, ↑ LFTs |
| **Bortezomib, ixazomib, carfilzomib** | Proteasome (induce arrest at G2-M phase → apoptosis) | Multiple myeloma, mantle cell lymphoma | Peripheral neuropathy, herpes zoster reactivation |
| **Vemurafenib, encorafenib, dabrafenib** | BRAF | Melanoma<br>Often co-administered with MEK inhibitors (eg, trametinib) | Rash, fatigue, nausea, diarrhea |
| **Palbociclib** | Cyclin-dependent kinase 4/6 (induces arrest at G1-S phase → apoptosis) | Breast cancer | Myelosuppression, pneumonitis |
| **Olaparib** | Poly(ADP-ribose) polymerase (↓ DNA repair) | Breast, ovarian, pancreatic, and prostate cancers | Myelosuppression, edema, diarrhea |

### Amelioration of adverse effects of chemotherapy

| DRUG | MECHANISM | CLINICAL USE |
|---|---|---|
| **Amifostine** | Free radical scavenger | Nephrotoxicity from platinum compounds |
| **Dexrazoxane** | Iron chelator | Cardiotoxicity from anthracyclines |
| **Leucovorin (folinic acid)** | Tetrahydrofolate precursor | Myelosuppression from methotrexate (leucovorin "rescue"); also enhances the effects of 5-FU |
| **Mesna** | Sulfhydryl compound that binds acrolein (toxic metabolite of cyclophosphamide/ifosfamide) | Hemorrhagic cystitis from cyclophosphamide/ifosfamide |
| **Rasburicase** | Recombinant uricase that catalyzes metabolism of uric acid to allantoin | Tumor lysis syndrome |
| **Ondansetron, granisetron** | 5-$HT_3$ receptor antagonists | Acute nausea and vomiting (usually within 1-2 hr after chemotherapy) |
| **Prochlorperazine, metoclopramide** | $D_2$ receptor antagonists | |
| **Aprepitant, fosaprepitant** | $NK_1$ receptor antagonists | Delayed nausea and vomiting (>24 hr after chemotherapy) |
| **Filgrastim, sargramostim** | Recombinant G(M)-CSF | Neutropenia |
| **Epoetin alfa** | Recombinant erythropoietin | Anemia |

## Key chemotoxicities




Cisplatin, Carboplatin → ototoxicity

Vincristine → peripheral neuropathy
Bleomycin, Busulfan → pulmonary fibrosis
Doxorubicin, Daunorubicin → cardiotoxicity
Trastuzumab → cardiotoxicity
Cisplatin, Carboplatin → nephrotoxicity

CYclophosphamide → hemorrhagic cystitis

Nonspecific common toxicities of nearly all cytotoxic chemotherapies include myelosuppression (neutropenia, anemia, thrombocytopenia), GI toxicity (nausea, vomiting, mucositis), alopecia.

HIGH-YIELD SYSTEMS

# Musculoskeletal, Skin, and Connective Tissue

*"Rigid, the skeleton of habit alone upholds the human frame."*

—Virginia Woolf, *Mrs. Dalloway*

*"Beauty may be skin deep, but ugly goes clear to the bone."*

—Redd Foxx

*"The finest clothing made is a person's own skin, but, of course, society demands something more than this."*

—Mark Twain

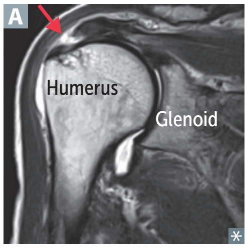
*"To thrive in life you need three bones. A wishbone. A backbone. And a funny bone."*

—Reba McEntire

This chapter provides information you will need to understand certain anatomical dysfunctions, rheumatic diseases, and dermatologic conditions. Be able to interpret 3D anatomy in the context of radiologic imaging. For the rheumatic diseases, create instructional cases or personas that include the most likely presentation and symptoms: risk factors, gender, important markers (eg, autoantibodies), and other epidemiologic factors. Doing so will allow you to answer the higher order questions that are likely to be asked on the exam.

## ▸ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—ANATOMY AND PHYSIOLOGY

### Rotator cuff muscles

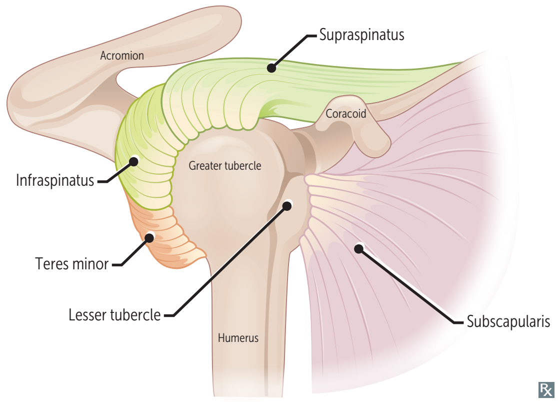



Shoulder muscles that form the rotator cuff:

- **S**upraspinatus (suprascapular nerve)—abducts arm initially (before the action of the deltoid); most common rotator cuff injury (trauma or degeneration and impingement → tendinopathy or tear [arrow in A]), assessed by "empty/full can" test
- **I**nfraspinatus (suprascapular nerve)—externally rotates arm; pitching injury
- **t**eres minor (axillary nerve)—adducts and externally rotates arm
- **S**ubscapularis (upper and lower subscapular nerves)—internally rotates and adducts arm

Innervated primarily by C5-C6.

**SItS** (**small** t is for teres **minor**).




### Arm abduction

| DEGREE | MUSCLE | NERVE |
|---|---|---|
| 0°–15° | Supraspinatus | Suprascapular |
| 15°–90° | Deltoid | Axillary |
| > 90° | Trapezius | Accessory |
| > 90° | **S**erratus **A**nterior | **L**ong **T**horacic (**SALT**) |

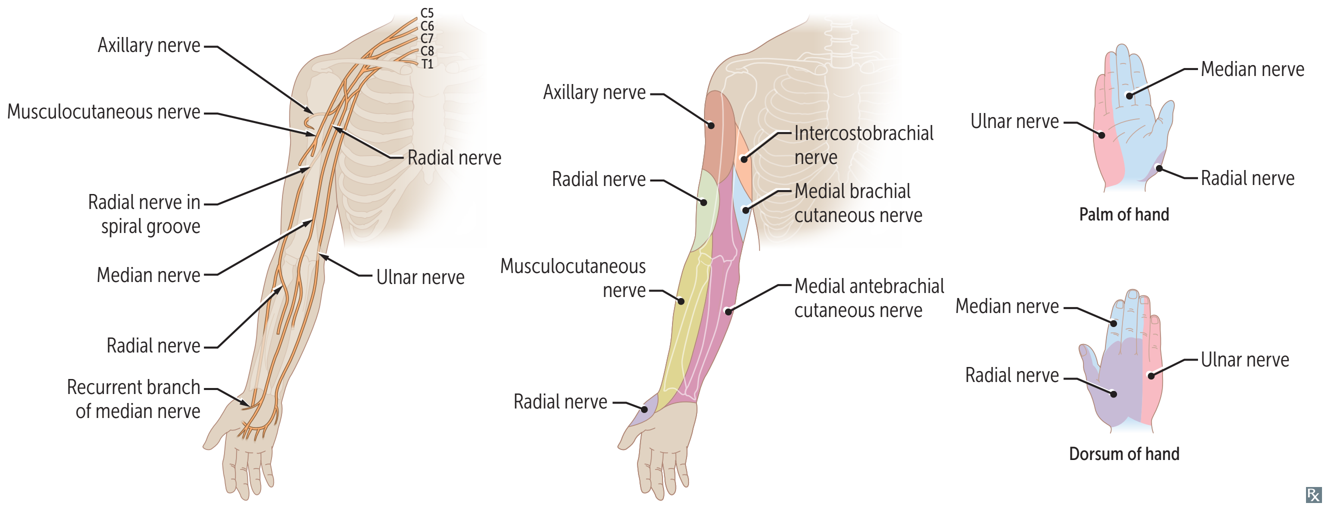
### Upper extremity nerves

| NERVE | CAUSES OF INJURY | PRESENTATION |
|---|---|---|
| Axillary (C5-C6) | Fractured surgical neck of humerus<br>Anterior dislocation of humerus | Flattened deltoid<br>Loss of arm abduction at shoulder (> 15°)<br>Loss of sensation over deltoid and lateral arm |
| Musculocutaneous (C5-C7) | Upper trunk compression | ↓ biceps (C5-6) reflex<br>Loss of forearm flexion and supination<br>Loss of sensation over radial and dorsal forearm |
| Radial (C5-T1) | Compression of axilla, eg, due to crutches or sleeping with arm over chair ("Saturday night palsy")<br>Midshaft fracture of humerus<br>Repetitive pronation/supination of forearm, eg, due to screwdriver use ("finger drop") | Injuries above the elbow cause loss of sensation over posterior arm/forearm and dorsal hand, wrist drop (loss of elbow, wrist, and finger extension) with ↓ grip strength (wrist extension necessary for maximal action of flexors)<br>Injuries below the elbow cause distal paresthesias without wrist drop<br>Tricep function and posterior arm sensation spared in midshaft fracture |

### Upper extremity nerves *(continued)*

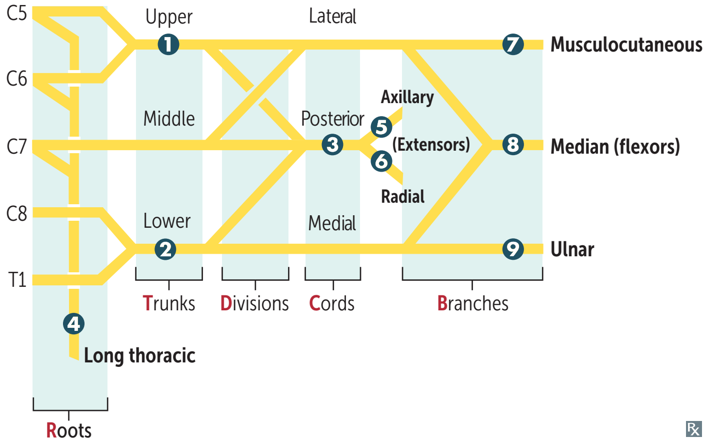
| NERVE | CAUSES OF INJURY | PRESENTATION |
|---|---|---|
| **Median (C5-T1)** | Supracondylar fracture of humerus → proximal lesion of the nerve<br>Carpal tunnel syndrome and wrist laceration → distal lesion of the nerve | "Ape hand" and "Hand of benediction"<br>Loss of wrist flexion and function of the lateral two **L**umbricals, **O**pponens pollicis, **A**bductor pollicis brevis, **F**lexor pollicis brevis (**LOAF**)<br>Loss of sensation over thenar eminence and dorsal and palmar aspects of lateral 3½ fingers with proximal lesion |
| **Ulnar (C8-T1)** | Fracture of medial epicondyle of humerus "funny bone" (proximal lesion)<br>Fractured hook of hamate (distal lesion) from fall on outstretched hand | "Ulnar claw" on digit extension<br>Radial deviation of wrist upon flexion (proximal lesion)<br>↓ flexion of ulnar fingers, abduction and adduction of fingers (interossei), thumb adduction, actions of ulnar 2 lumbrical muscles<br>Loss of sensation over ulnar 1½ fingers including hypothenar eminence |
| **Recurrent branch of median nerve (C5-T1)** | Superficial laceration of palm | "Ape hand"<br>Loss of thenar muscle group: opposition, abduction, and flexion of thumb<br>No loss of sensation |

Humerus fractures, proximally to distally, follow the **ARM** (**A**xillary → **R**adial → **M**edian)

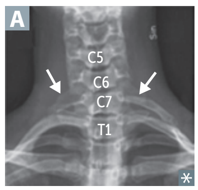


## Brachial plexus lesions

1. Erb palsy ("waiter's tip")
2. Klumpke palsy (claw hand)
3. Wrist drop
4. Winged scapula
5. Deltoid paralysis
6. "Saturday night palsy" (wrist drop)
7. Difficulty flexing elbow, variable sensory loss
8. Decreased thumb function, "hand of benediction"
9. Intrinsic muscles of hand, claw hand




Divisions of brachial plexus:
Randy
Travis
Drinks
Cold
Beer

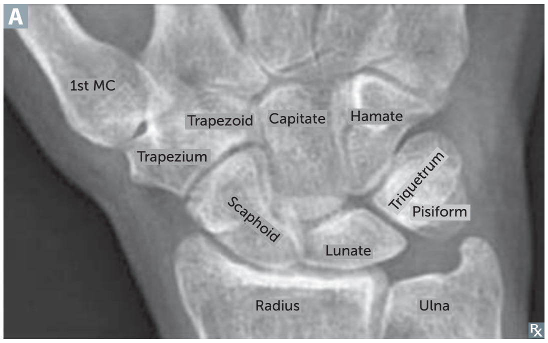
| CONDITION | INJURY | CAUSES | MUSCLE DEFICIT | FUNCTIONAL DEFICIT | PRESENTATION |
|---|---|---|---|---|---|
| **Erb palsy ("waiter's tip")** | Traction or tear of **upper** trunk: C5-C6 roots | Infants—lateral traction on neck during delivery<br>Adults—trauma | Deltoid, supraspinatus | Abduction (arm hangs by side) |  |
| | | | Infraspinatus, supraspinatus | Lateral rotation (arm medially rotated) | |
| | | | Biceps brachii<br>Herb gets DIBs on tips | Flexion, supination (arm extended and pronated) | |
| **Klumpke palsy** | Traction or tear of **lower** trunk: C8-T1 roots | Infants—upward force on arm during delivery<br>Adults—trauma (eg, grabbing a tree branch to break a fall) | Intrinsic hand muscles: lumbricals, interossei, thenar, hypothenar | Claw hand: lumbricals normally flex MCP joints and extend DIP and PIP joints |  |
| **Thoracic outlet syndrome** | Compression of **lower** trunk and subclavian vessels, most commonly within the scalene triangle | Cervical rib (arrows in A), Pancoast tumor | Same as Klumpke palsy | Atrophy of intrinsic hand muscles; ischemia, pain, and edema due to vascular compression |  |
| **Winged scapula** | Lesion of long thoracic nerve, roots C5-C7 ("wings of heaven") | Axillary node dissection after mastectomy, stab wounds | Serratus anterior | Inability to anchor scapula to thoracic cage → cannot abduct arm above horizontal position B |  |

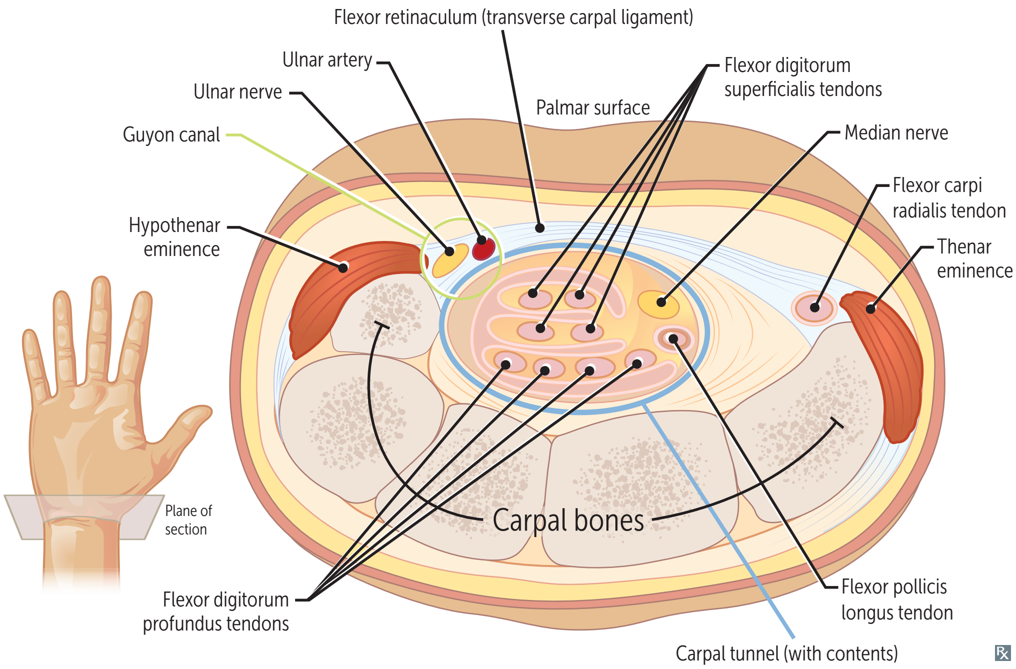
## Wrist region


**S**caphoid, **l**unate, **t**riquetrum, **p**isiform, **h**amate, **c**apitate, **t**rapezoid, **t**rapezium A. (**S**o **l**ong **t**o **p**inky, **h**ere **c**omes **t**he **t**humb)

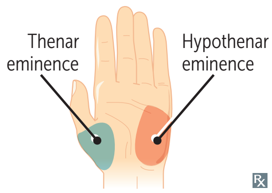
Scaphoid (palpable in anatomic snuff box B) is the most commonly fractured carpal bone, typically due to a fall on an outstretched hand. Complications of proximal scaphoid fractures include avascular necrosis and nonunion due to retrograde blood supply from a branch of the radial artery. Occult fracture not always seen on initial x-ray.

Dislocation of lunate may impinge median nerve and cause carpal tunnel syndrome.



## Hand muscles




Thenar (median)—**O**pponens pollicis, **A**bductor pollicis brevis, **F**lexor pollicis brevis, superficial head (deep head by ulnar nerve).

Hypothenar (ulnar)—**O**pponens digiti minimi, **A**bductor digiti minimi, **F**lexor digiti minimi brevis.

Both groups perform the same functions: **O**ppose, **A**bduct, and **F**lex (**OAF**).

Dorsal interossei (ulnar)—abduct the fingers. **DAB** = **D**orsals **AB**duct.

Palmar interossei (ulnar)—adduct the fingers. **PAD** = **P**almars **AD**duct.

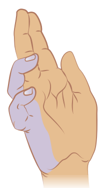
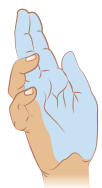
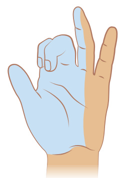
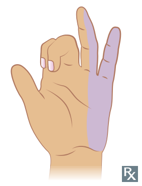
Lumbricals (1st/2nd, median; 3rd/4th, ulnar)—flex at the MCP joint, extend PIP and DIP joints.

## Distortions of the hand

At rest, a balance exists between the extrinsic flexors and extensors of the hand, as well as the intrinsic muscles of the hand—particularly the lumbrical muscles (flexion of MCP, extension of DIP and PIP joints).

"Clawing"—seen best with **distal** lesions of median or ulnar nerves. Remaining extrinsic flexors of the digits exaggerate the loss of the lumbricals → fingers extend at MCP, flex at DIP and PIP joints.

Deficits less pronounced in **proximal** lesions; deficits present during voluntary flexion of the digits.

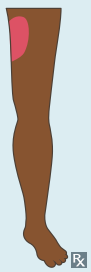
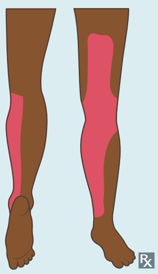
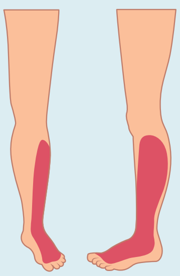
| SIGN | "Ulnar claw" | "Hand of benediction" | "Median claw" | "OK gesture" |
|---|---|---|---|---|
| PRESENTATION |  |  |  |  |
| CONTEXT | Extending fingers/at rest | Making a fist | Extending fingers/at rest | Making a fist |
| LOCATION OF LESION | Distal ulnar nerve | Proximal median nerve | Distal median nerve | Proximal ulnar nerve |

Note: Atrophy of the thenar eminence can be seen in median nerve lesions, while atrophy of the hypothenar eminence can be seen in ulnar nerve lesions.

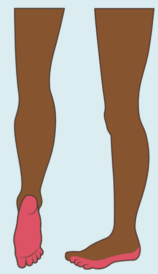
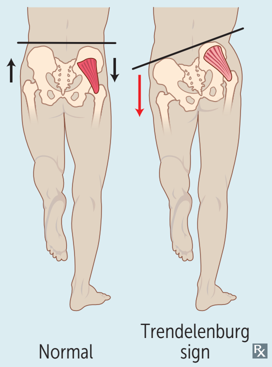
**Actions of hip muscles**

| ACTION | MUSCLES |
|---|---|
| **Abductors** | Gluteus medius, gluteus minimus |
| **Adductors** | Adductor magnus, adductor longus, adductor brevis |
| **Extensors** | Gluteus maximus, semitendinosus, semimembranosus |
| **Flexors** | Iliopsoas, rectus femoris, tensor fascia lata, pectineus, sartorius |
| **Internal rotation** | Gluteus medius, gluteus minimus, tensor fascia latae |
| **External rotation** | Iliopsoas, gluteus maximus, piriformis, obturator |

## Lower extremity nerves

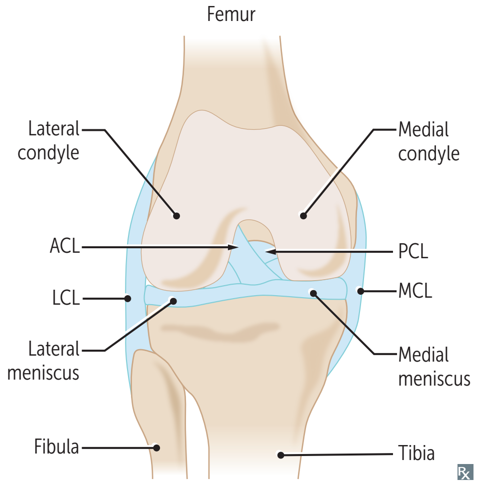
| NERVE | INNERVATION | CAUSE OF INJURY | PRESENTATION/COMMENTS |
|---|---|---|---|
| **Iliohypogastric (T12-L1)** | Sensory—suprapubic region<br>Motor—transversus abdominis and internal oblique | Abdominal surgery | Burning or tingling pain in surgical incision site radiating to inguinal and suprapubic region |
| **Genitofemoral nerve (L1-L2)** | Sensory—scrotum/labia majora, medial thigh<br>Motor—cremaster | Laparoscopic surgery | ↓ upper medial thigh and anterior thigh sensation beneath the inguinal ligament (lateral part of the femoral triangle); absent cremasteric reflex |
| **Lateral femoral cutaneous (L2-L3)** | Sensory—anterior and lateral thigh | Tight clothing, obesity, pregnancy, pelvic procedures | ↓ thigh sensation (anterior and lateral) |
| **Obturator (L2-L4)**<br> | Sensory—medial thigh<br>Motor—obturator externus, adductor longus, adductor brevis, gracilis, pectineus, adductor magnus | Pelvic surgery | ↓ thigh sensation (medial) and adduction |
| **Femoral (L2-L4)**<br> | Sensory—anterior thigh, medial leg<br>Motor—quadriceps, iliacus, pectineus, sartorius | Pelvic fracture | ↓ leg extension (↓ patellar reflex) |
| **Sciatic (L4-S3)** | Motor—semitendinosus, semimembranosus, biceps femoris, adductor magnus | Herniated disc, posterior hip dislocation | Splits into common peroneal and tibial nerves |
| **Common (fibular) peroneal (L4-S2)**<br> | Superficial peroneal nerve:<br>▪ Sensory—dorsum of foot (except webspace between hallux and 2nd digit)<br>▪ Motor—peroneus longus and brevis<br>Deep peroneal nerve:<br>▪ Sensory—webspace between hallux and 2nd digit<br>▪ Motor—tibialis anterior | Trauma or compression of lateral aspect of leg, fibular neck fracture | PED = Peroneal Everts and Dorsiflexes; if injured, foot dropPED<br>Loss of sensation on dorsum of foot<br>Foot drop—inverted and plantarflexed at rest, loss of eversion and dorsiflexion; “steppage gait” |

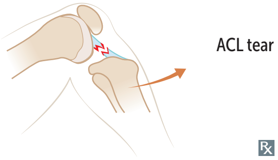
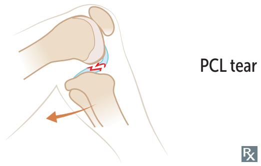
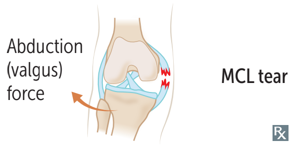
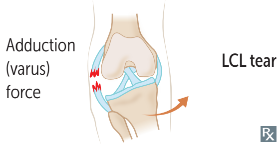
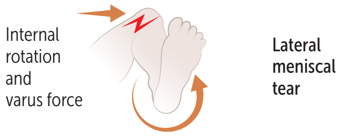
### Lower extremity nerves *(continued)*

| NERVE | INNERVATION | CAUSE OF INJURY | PRESENTATION/COMMENTS |
|---|---|---|---|
| **Tibial (L4-S3)**<br> | Sensory—sole of foot<br>Motor—biceps femoris (long head), triceps surae, plantaris, popliteus, flexor muscles of foot | Knee trauma, Baker cyst (proximal lesion); tarsal tunnel syndrome (distal lesion) | **TIP** = **T**ibial **I**nverts and **P**lantarflexes; if injured, can't stand on **TIP**toes<br>Inability to curl toes and loss of sensation on sole; in proximal lesions, foot everted at rest with weakened inversion and plantar flexion |
| **Superior gluteal (L4-S1)**<br> | Motor—gluteus medius, gluteus minimus, tensor fascia latae | Iatrogenic injury during intramuscular injection to superomedial gluteal region (prevent by choosing superolateral quadrant, preferably anterolateral region) | Trendelenburg sign/gait—pelvis tilts because weight-bearing leg cannot maintain alignment of pelvis through hip abduction<br>Lesion is contralateral to the side of the hip that drops, ipsilateral to extremity on which the patient stands |
| **Inferior gluteal (L5-S2)** | Motor—gluteus maximus | Posterior hip dislocation | Difficulty climbing stairs, rising from seated position; loss of hip extension |
| **Pudendal (S2-S4)** | Sensory—perineum<br>Motor—external urethral and anal sphincters | Stretch injury during childbirth, prolonged cycling, horseback riding | ↓ sensation in perineum and genital area; can cause fecal and/or urinary incontinence<br>Can be blocked with local anesthetic during childbirth using ischial spine as a landmark for injection |

## Knee exam

**L**ateral femoral condyle to anterior tibia: **A**CL.
**M**edial femoral condyle to posterior tibia: **P**CL.
**LAMP**.

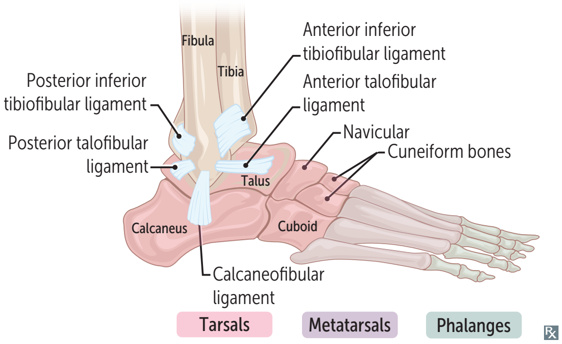



| TEST | PROCEDURE | |
|---|---|---|
| **Anterior drawer sign** | Bending knee at 90° angle, ↑ anterior gliding of tibia (relative to femur) due to ACL injury<br>Lachman test also tests ACL, but is more sensitive (↑ anterior gliding of tibia [relative to femur] with knee bent at 30° angle) |  |
| **Posterior drawer sign** | Bending knee at 90° angle, ↑ posterior gliding of tibia due to PCL injury |  |
| **Abnormal passive abduction** | Also called valgus stress test.<br>Knee either extended or at ~ 30° angle, lateral (valgus) force → medial space widening of tibia → MCL injury |  |
| **Abnormal passive adduction** | Also called varus stress test.<br>Knee either extended or at ~ 30° angle, medial (varus) force → lateral space widening of tibia → LCL injury |  |
| **McMurray test** | During flexion and extension of knee with rotation of tibia/foot (**LIME**):<br>▪ Pain, "popping" on internal rotation and varus force → **L**ateral meniscal tear (**I**nternal rotation stresses lateral meniscus)<br>▪ Pain, "popping" on external rotation and valgus force → **M**edial meniscal tear (**E**xternal rotation stresses medial meniscus) | <br> |

## Ankle sprains

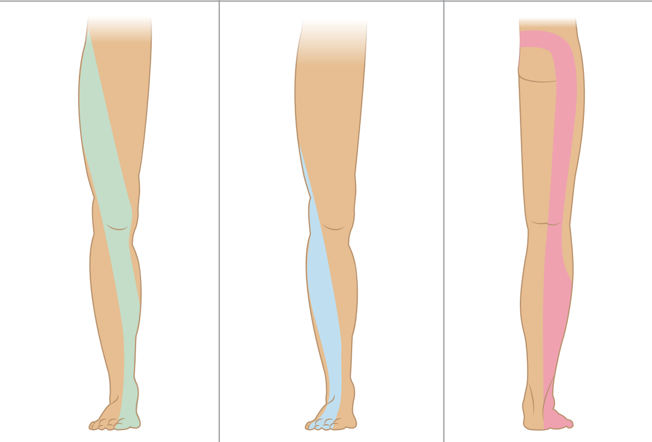
**A**nterior **t**alo**f**ibular ligament—most common ankle sprain overall, classified as a low ankle sprain. Due to overinversion/supination of foot. **A**lways **t**ears **f**irst.

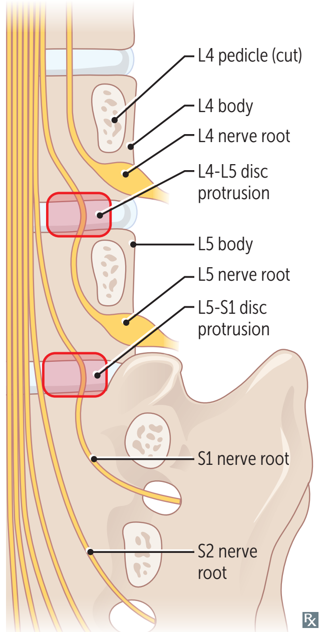
Anterior inferior tibiofibular ligament—most common high ankle sprain.




## Signs of lumbosacral radiculopathy

Paresthesia and weakness related to specific lumbosacral spinal nerves. Intervertebral disc (nucleus pulposus) herniates posterolaterally through annulus fibrosus (outer ring) into central canal due to thin posterior longitudinal ligament and thicker anterior longitudinal ligament along midline of vertebral bodies. Nerve affected is usually below the level of herniation.

| Disc level herniation | L3-L4 | L4-L5 | L5-S1 |
|---|---|---|---|
| Nerve root affected | L4 | L5 | S1 |
| Dermatome affected |  | | |
| Clinical findings | Weakness of knee extension<br>↓patellar reflex | Weakness of dorsiflexion<br>Difficulty in heel walking | Weakness of plantar flexion<br>Difficulty in toe walking<br>↓Achilles reflex |



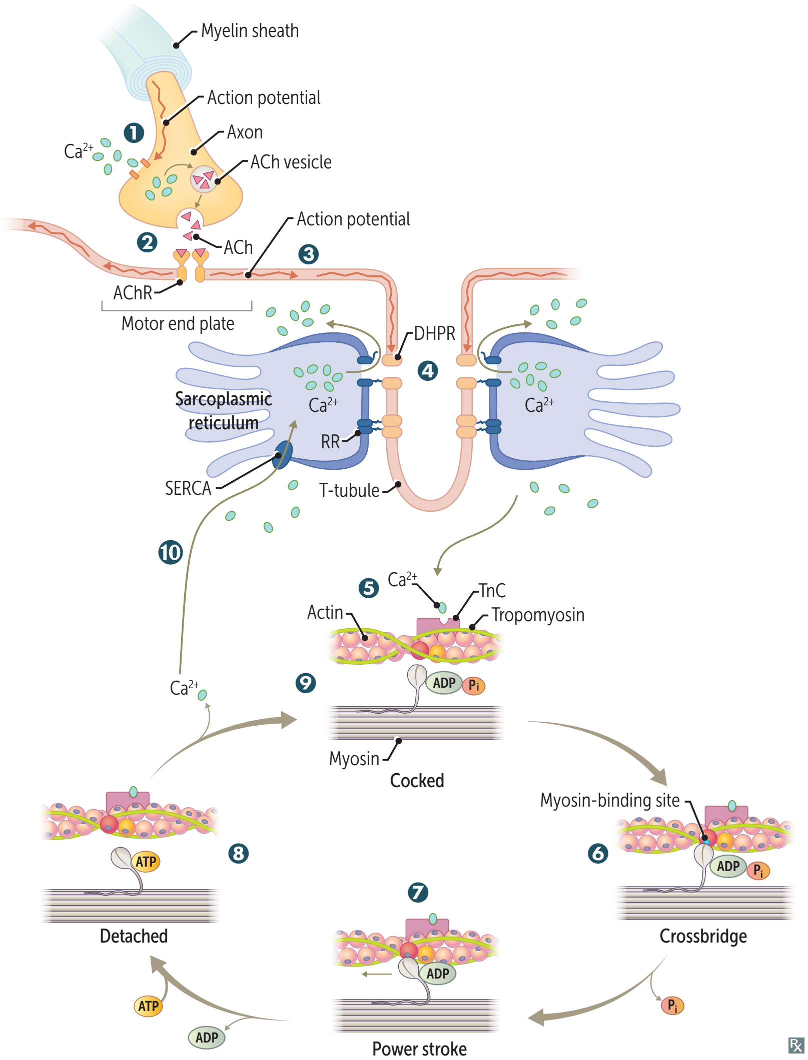

## Neurovascular pairing

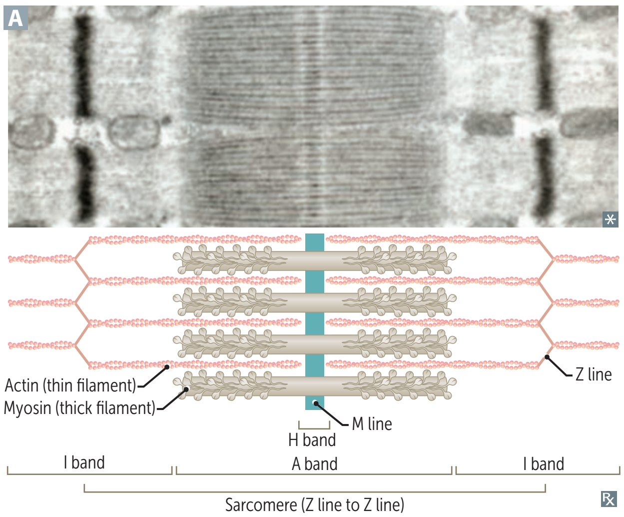
Nerves and arteries are frequently named together by the bones/regions with which they are associated. The following are exceptions to this naming convention.

| LOCATION | NERVE | ARTERY |
|---|---|---|
| **Axilla/lateral thorax** | Long thoracic | Lateral thoracic |
| **Surgical neck of humerus** | Axillary | Posterior circumflex |
| **Midshaft of humerus** | Radial | Deep brachial |
| **Distal humerus/cubital fossa** | Median | Brachial |
| **Popliteal fossa** | Tibial | Popliteal |
| **Posterior to medial malleolus** | Tibial | Posterior tibial |

**Motoneuron action potential to muscle contraction**

T-tubules are extensions of plasma membrane in contact with the sarcoplasmic reticulum, allowing for coordinated contraction of striated muscles.




❶ Action potential opens presynaptic voltage-gated $Ca^{2+}$ channels, inducing acetylcholine (ACh) release.

❷ Postsynaptic ACh binding leads to muscle cell depolarization at the motor end plate.

❸ Depolarization travels over the entire muscle cell and deep into the muscle via the T-tubules.

❹ Membrane depolarization induces conformational changes in the voltage-sensitive dihydropyridine receptor (DHPR) and its mechanically coupled ryanodine receptor (RR) → $Ca^{2+}$ release from the sarcoplasmic reticulum into the cytoplasm.

❺ Tropomyosin is blocking myosin-binding sites on the actin filament. Released $Ca^{2+}$ binds to troponin C (TnC), shifting tropomyosin to expose the myosin-binding sites.

❻ The myosin head binds strongly to actin, forming a crossbridge. $P_i$ is then released, initiating the power stroke.

❼ During the power stroke, force is produced as myosin pulls on the thin filament **A**. Muscle shortening occurs, with shortening of **H** and **I** bands and between **Z** lines (**HIZ** shrinkage). The A band remains the same length (**A** band is **A**lways the same length). ADP is released at the end of the power stroke.

❽ Binding of new ATP molecule causes detachment of myosin head from actin filament. $Ca^{2+}$ is resequestered.

❾ ATP hydrolysis into ADP and $P_i$ results in myosin head returning to high-energy position (cocked). The myosin head can bind to a new site on actin to form a crossbridge if $Ca^{2+}$ remains available.

❿ Reuptake of calcium by sarco(endo)plasmic reticulum $Ca^{2+}$ ATPase (SERCA) → muscle relaxation.

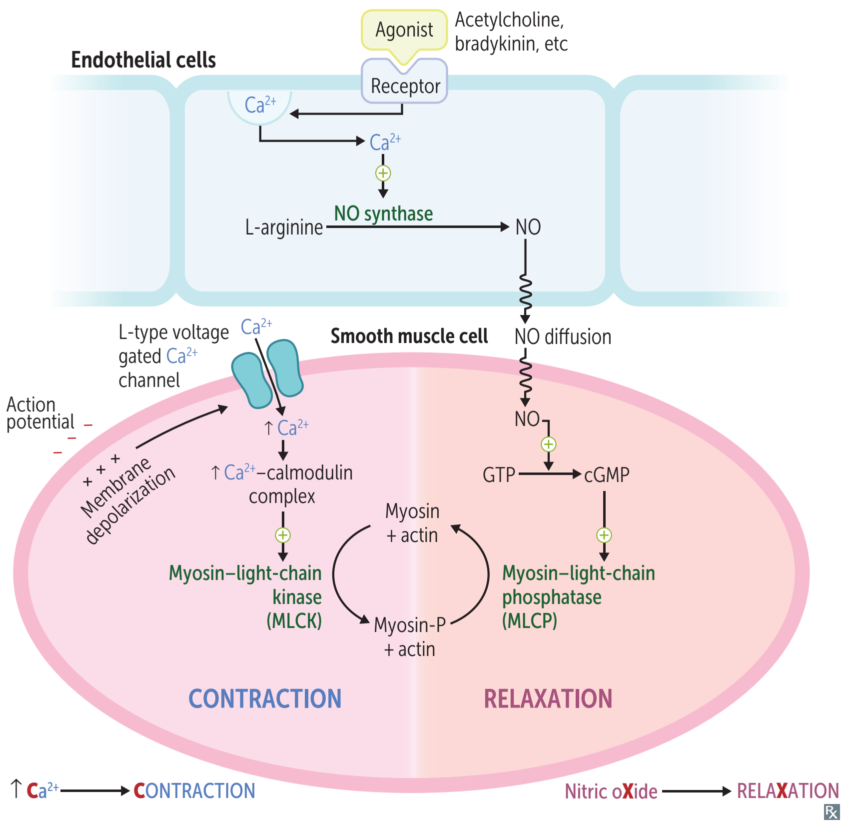
## Types of skeletal muscle fibers

| | Type I | Type II |
|---|---|---|
| CONTRACTION VELOCITY | Slow | Fast |
| FIBER COLOR | Red | White |
| PREDOMINANT METABOLISM | Oxidative phosphorylation → sustained contraction | Anaerobic glycolysis |
| MITOCHONDRIA, MYOGLOBIN | ↑ | ↓ |
| TYPE OF TRAINING | Endurance training | Weight/resistance training, sprinting |
| NOTES | Think "1 slow red ox" | Think "2 fast white antelopes" |

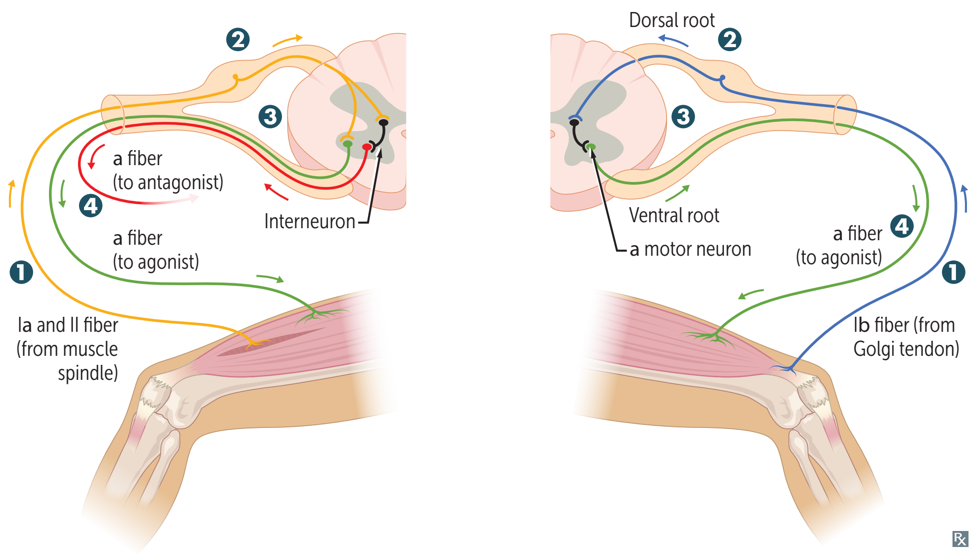
## Skeletal muscle adaptations

| | Atrophy | Hypertrophy |
|---|---|---|
| MYOFIBRILS | ↓ (removal via ubiquitin-proteasome system) | ↑ (addition of sarcomeres in parallel) |
| MYONUCLEI | ↓ (selective apoptosis) | ↑ (fusion of satellite cells) |

## Vascular smooth muscle contraction and relaxation



| **Muscle proprioceptors** | Specialized sensory receptors that relay information about muscle dynamics. | |
|---|---|---|
| | **Muscle stretch receptors** | **Golgi tendon organ** |
| PATHWAY | ❶ ↑ length and speed of stretch → ❷ via dorsal root ganglion (DRG) → ❸ activation of inhibitory interneuron and α motor neuron → ❹ simultaneous inhibition of antagonist muscle (prevents overstretching) and activation of agonist muscle (contraction). | ❶ ↑ tension → ❷ via DRG → ❸ activation of inhibitory interneuron → ❹ inhibition of agonist muscle (reduced tension within muscle and tendon) |
| LOCATION/INNERVATION | Body of muscle/type Ia and II sensory axons | Tendons/type Ib sensory axons |
| ACTIVATION BY | ↑ muscle stretch. Responsible for deep tendon reflexes | ↑ muscle tension |

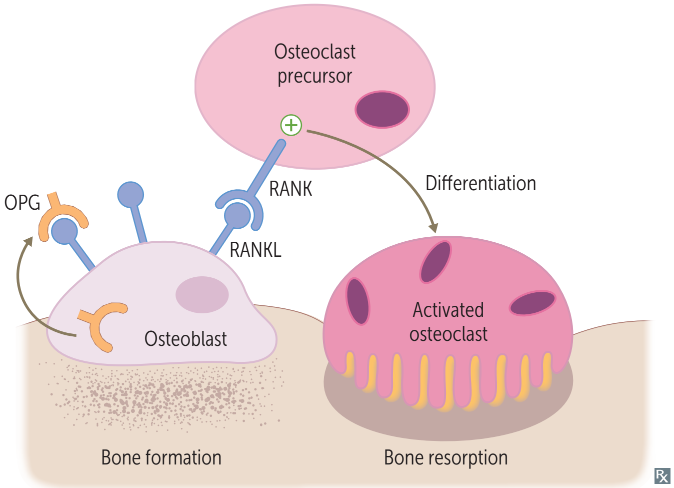



## Bone formation

| | |
|---|---|
| **Endochondral ossification** | Bones of axial skeleton, appendicular skeleton, and base of skull. Cartilaginous model of bone is first made by chondrocytes. Osteoclasts and osteoblasts later replace with woven bone and then remodel to lamellar bone. In adults, woven bone occurs after fractures and in Paget disease. Defective in achondroplasia. |
| **Membranous ossification** | Bones of calvarium, facial bones, and clavicle. Woven bone formed directly without cartilage. Later remodeled to lamellar bone. |

## Cell biology of bone

| | |
|---|---|
| **Osteoblast** | Builds bone by secreting collagen and catalyzing mineralization in alkaline environment via ALP. Differentiates from mesenchymal stem cells in periosteum. Osteoblastic activity measured by bone ALP, osteocalcin, propeptides of type I procollagen. |
| **Osteoclast** | Dissolves ("crushes") bone by secreting $H^+$ and collagenases. Differentiates from a fusion of monocyte/macrophage lineage precursors. RANK receptors on osteoclasts are stimulated by RANKL (RANK ligand, expressed on osteoblasts). OPG (osteoprotegerin, a RANKL decoy receptor) binds RANKL to prevent RANK-RANKL interaction → ↓ osteoclast activity. |
| **Parathyroid hormone** | At low, intermittent levels, exerts anabolic effects (building bone) on osteoblasts and osteoclasts (indirect). Chronically ↑ PTH levels (1° hyperparathyroidism) cause catabolic effects (osteitis fibrosa cystica). |
| **Estrogen** | Inhibits apoptosis in bone-forming osteoblasts and induces apoptosis in bone-resorbing osteoclasts. Causes closure of epiphyseal plate during puberty. Estrogen deficiency (surgical or postmenopausal) → ↑ cycles of remodeling and bone resorption → ↑ risk of osteoporosis. |




▶ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PATHOLOGY

## Overuse injuries of the elbow

| | |
|---|---|
| **Medial epicondylitis (golfer's elbow)** | Repetitive flexion or idiopathic → pain near medial epicondyle. |
| **Lateral epicondylitis (tennis elbow)** | Repetitive extension (backhand shots) or idiopathic → pain near lateral epicondyle. |

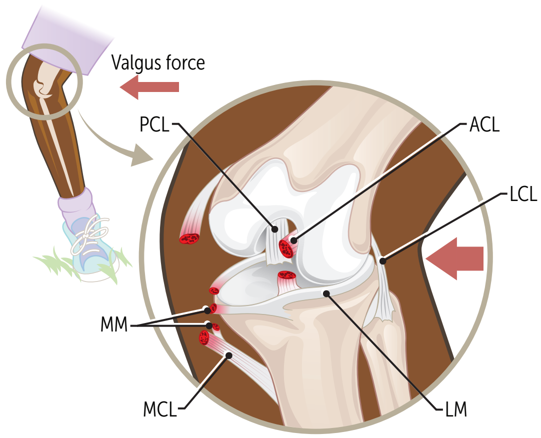
| | | |
|---|---|---|
| **Clavicle fractures** | Common in children and as birth trauma. Usually caused by a fall on outstretched hand or by direct trauma to shoulder. Weakest point at the junction of middle and lateral thirds; fractures at the middle third segment are most common A. Presents as shoulder drop, shortened clavicle (lateral fragment is depressed due to arm weight and medially rotated by arm adductors [eg, pectoralis major]). |  |

**Wrist and hand injuries**

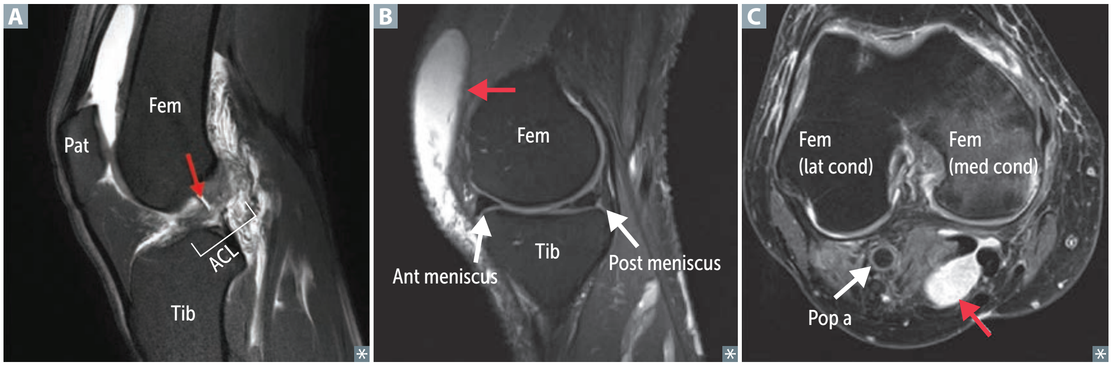
| | | |
|---|---|---|
| **Guyon canal syndrome** | Compression of ulnar nerve at wrist. Classically seen in cyclists due to pressure from handlebars. | |
| **Carpal tunnel syndrome**  | Entrapment of median nerve in carpal tunnel (between transverse carpal ligament and carpal bones) → nerve compression → paresthesia, pain, and numbness in distribution of median nerve. Thenar eminence atrophies A but sensation spared, because palmar cutaneous branch enters hand external to carpal tunnel. | Suggested by ⊕ Tinel sign (percussion of wrist causes tingling) and Phalen maneuver (90° flexion of wrist causes tingling). Associated with pregnancy (due to edema), rheumatoid arthritis, hypothyroidism, diabetes, acromegaly, dialysis-related amyloidosis; may be associated with repetitive use. |
| **Metacarpal neck fracture**  | Also called boxer's fracture. Common fracture caused by direct blow with a closed fist (eg, from punching a wall). Most commonly seen in the 5th metacarpal B. | |

## Common knee conditions

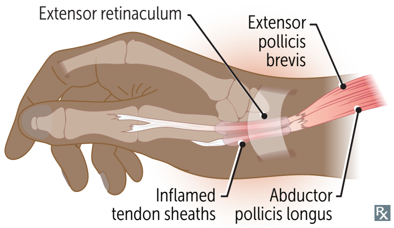
| | |
|---|---|
| **"Unhappy triad"** | Common injury in contact sports due to laterally directed force to a planted foot. Consists of damage to the ACL A, MCL, and medial meniscus (attached to MCL). However, lateral meniscus involvement is more common than medial meniscus involvement in conjunction with ACL and MCL injury. Presents with acute pain and signs of joint instability. |
| **Prepatellar bursitis** | Inflammation of the prepatellar bursa in front of the kneecap (red arrow in B). Can be caused by repeated trauma or pressure from excessive kneeling (also called "housemaid's knee"). |
| **Popliteal cyst** | Also called Baker cyst. Popliteal fluid collection (red arrow in C) in gastrocnemius-semimembranosus bursa commonly communicating with synovial space and related to chronic joint disease (eg, osteoarthritis, rheumatoid arthritis). |



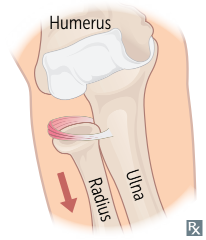
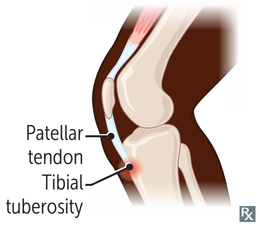
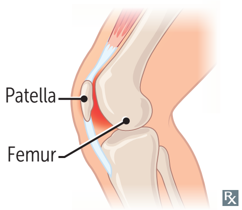
Anterior view of left knee



## Common musculoskeletal conditions

| | |
|---|---|
| **De Quervain tenosynovitis** | Noninflammatory thickening of abductor pollicis longus and extensor pollicis brevis tendons → pain or tenderness at radial styloid. ⊕ Finkelstein test (pain at radial styloid with active or passive stretch of thumb tendons). ↑ risk in new parent (lifting baby), golfers, racquet sport players, "thumb" texters.   |
| **Ganglion cyst** | Fluid-filled swelling overlying joint or tendon sheath, most commonly at dorsal side of wrist. Arises from herniation of dense connective tissue. Usually resolves spontaneously. |
| **Iliotibial band syndrome** | Overuse injury of lateral knee that occurs primarily in runners. Pain develops 2° to friction of iliotibial band against lateral femoral epicondyle. |
| **Limb compartment syndrome** | ↑ pressure within fascial compartment of a limb → venous outflow obstruction and arteriolar collapse → anoxia and necrosis. Causes include significant long bone fractures, reperfusion injury, animal venoms. Presents with severe pain and tense, swollen compartments with passive stretch of muscles in the affected compartment. Increased serum creatine kinase and motor deficits are late signs of irreversible muscle and nerve damage. 5 Ps: pain, palor, paresthesia, pulselessness, paralysis. |
| **Medial tibial stress syndrome** | Also called shin splints. Common cause of shin pain and diffuse tenderness in runners and military recruits. Caused by bone resorption that outpaces bone formation in tibial cortex. |
| **Plantar fasciitis** | Inflammation of plantar aponeurosis characterized by heel pain (worse with first steps in the morning or after period of inactivity) and tenderness. |
| **Temporomandibular disorders** | Group of disorders that involve the temporomandibular joint (TMJ) and muscles of mastication. Multifactorial etiology; associated with TMJ trauma, poor head and neck posture, abnormal trigeminal nerve pain processing, psychological factors. Present with dull, constant unilateral facial pain that worsens with jaw movement, otalgia, headache, TMJ dysfunction (eg, limited range of motion). |

## Childhood musculoskeletal conditions

| | |
|---|---|
| **Radial head subluxation**   | Also called nursemaid's elbow. Common elbow injury in children < 5 years. Caused by a sudden pull on the arm → immature annular ligament slips over head of radius. Injured arm held in slightly flexed and pronated position. |
| **Osgood-Schlatter disease**   | Also called traction apophysitis. Overuse injury caused by repetitive strain and chronic avulsion of the secondary ossification center of proximal tibial tubercle. Occurs in adolescents after growth spurt. Common in running and jumping athletes. Presents with progressive anterior knee pain. |
| **Patellofemoral syndrome**   | Overuse injury that commonly presents in young, female athletes as anterior knee pain. Exacerbated by prolonged sitting or weight-bearing on a flexed knee. |
| **Developmental dysplasia of the hip** | Abnormal acetabulum development in newborns. Risk factor is breech presentation. Results in hip instability/dislocation. Commonly tested with Ortolani and Barlow maneuvers (manipulation of newborn hip reveals a "clunk"). Confirmed via ultrasound (x-ray not used until ~4–6 months because cartilage is not ossified). |
| **Legg-Calvé-Perthes disease** | Idiopathic avascular necrosis of femoral head. Commonly presents between 5–7 years with insidious onset of hip pain that may cause child to limp. More common in males (4:1 ratio). Initial x-ray often normal. |
| **Slipped capital femoral epiphysis** | Classically presents in an obese young adolescent with hip/knee pain and altered gait. Increased axial force on femoral head → epiphysis displaces relative to femoral neck (like a scoop of ice cream slipping off a cone). Diagnosed via x-ray. |

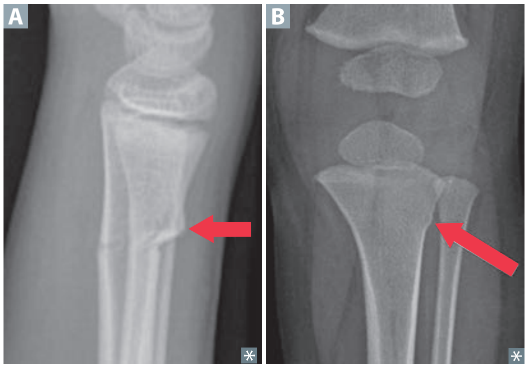
## Common pediatric fractures

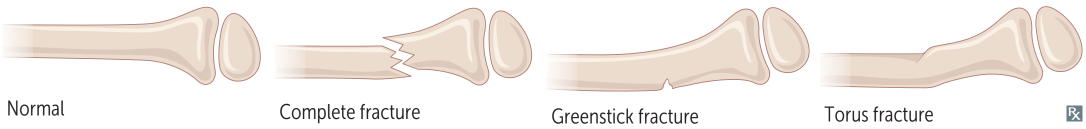
**Greenstick fracture**

Incomplete fracture extending partway through width of bone A following bending stress; bone fails on tension side; compression side intact (compare to torus fracture). Bone is bent like a **green twig**.

**Torus (buckle) fracture**

Axial force applied to immature bone → cortex buckles on compression (concave) side and fractures B. **T**ension (convex) side **r**emains **s**olid (intact).

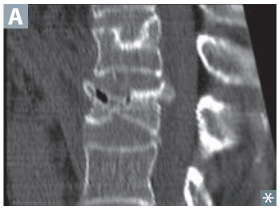



## Achondroplasia

Failure of longitudinal bone growth (endochondral ossification) → short limbs. Membranous ossification is not affected → large head relative to limbs. Constitutive activation of fibroblast growth factor receptor (FGFR3) actually inhibits chondrocyte proliferation. > 85% of mutations occur sporadically; autosomal dominant with full penetrance (homozygosity is lethal). Associated with ↑ paternal age. Most common cause of short-limbed dwarfism.

## Osteoporosis




Trabecular (spongy) and cortical bone lose mass despite normal bone mineralization and lab values (serum $Ca^{2+}$ and $PO_4^{3-}$).

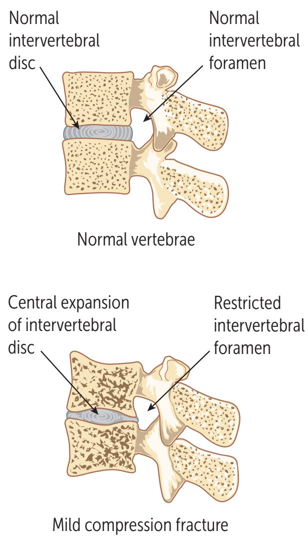
Most commonly due to ↑ bone resorption related to ↓ estrogen levels and old age. Can be 2° to drugs (eg, steroids, alcohol, anticonvulsants, anticoagulants, thyroid replacement therapy) or other conditions (eg, hyperparathyroidism, hyperthyroidism, multiple myeloma, malabsorption syndromes, anorexia).

Diagnosed by bone mineral density measurement by DEXA (dual-energy X-ray absorptiometry) at the lumbar spine, total hip, and femoral neck, with a T-score of ≤ –2.5 or by a fragility fracture (eg, fall from standing height, minimal trauma) at hip or vertebra. One-time screening recommended in females ≥ 65 years old.

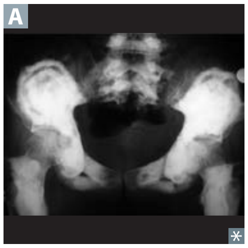
Prophylaxis: regular weight-bearing exercise and adequate $Ca^{2+}$ and vitamin D intake throughout adulthood.

Treatment: bisphosphonates, teriparatide, SERMs, rarely calcitonin; denosumab (monoclonal antibody against RANKL).

Can lead to vertebral compression fractures A—acute back pain, loss of height, kyphosis. Also can present with fractures of femoral neck, distal radius (Colles fracture).



## Osteopetrosis



Failure of normal bone resorption due to defective osteoclasts → thickened, dense bones that are prone to fracture. Mutations (eg, carbonic anhydrase II) impair ability of osteoclast to generate acidic environment necessary for bone resorption. Overgrowth of cortical bone fills marrow space → pancytopenia, extramedullary hematopoiesis. Can result in cranial nerve impingement and palsies due to narrowed foramina.

X-rays show diffuse symmetric sclerosis (bone-in-bone, "stone bone" A). Bone marrow transplant is potentially curative as osteoclasts are derived from monocytes.

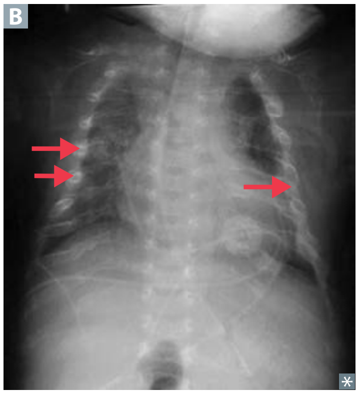
## Osteomalacia/rickets

Defective mineralization of osteoid (osteomalacia) or cartilaginous growth plates (rickets, only in children). Most commonly due to vitamin D deficiency.

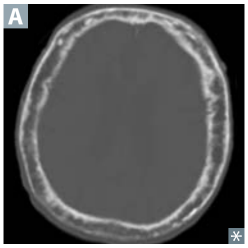
X-rays show osteopenia and pseudofractures in osteomalacia, epiphyseal widening and metaphyseal cupping/fraying in rickets. Children with rickets have pathologic bow legs (genu varum A), bead-like costochondral junctions (rachitic rosary B), craniotabes (soft skull).

↓ vitamin D → ↓ serum $Ca^{2+}$ → ↑ PTH secretion → ↓ serum $PO_4^{3-}$.

Hyperactivity of osteoblasts → ↑ ALP.



## Osteitis deformans



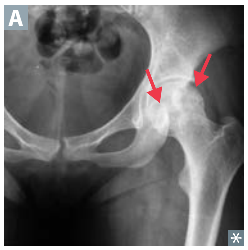
Also called Paget disease of bone. Common, localized disorder of bone remodeling caused by ↑ osteoclastic activity followed by ↑ osteoblastic activity that forms poor-quality bone. Serum $Ca^{2+}$, phosphorus, and PTH levels are normal. ↑ ALP. Mosaic pattern of woven and lamellar bone (osteocytes within lacunae in chaotic juxtapositions); long bone chalk-stick fractures. ↑ blood flow from ↑ arteriovenous shunts may cause high-output heart failure. ↑ risk of osteosarcoma.

Hat size can be increased due to skull thickening A; hearing loss is common due to skull deformity.

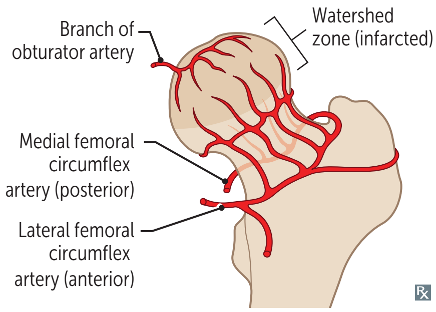
Stages of Paget disease:
- Lytic—osteoclasts
- Mixed—osteoclasts + osteoblasts
- Sclerotic—osteoblasts
- Quiescent—minimal osteoclast/osteoblast activity

Treatment: bisphosphonates.

## Avascular necrosis of bone



Infarction of bone and marrow, usually very painful. Most common site is femoral head (watershed zone) A (due to insufficiency of medial circumflex femoral artery). Causes include **C**orticosteroids, chronic **A**lcohol overuse, **S**ickle cell disease, **T**rauma, **S**LE, "the **B**ends" (caisson/decompression disease), **LE**gg-Calvé-Perthes disease (idiopathic), **G**aucher disease, **S**lipped capital femoral epiphysis—**CASTS B**end **LEGS**.



## Lab values in bone disorders

| DISORDER | SERUM $Ca^{2+}$ | $PO_4^{3-}$ | ALP | PTH | COMMENTS |
|---|---|---|---|---|---|
| **Osteoporosis** | — | — | — | — | ↓ bone mass |
| **Osteopetrosis** | —/↓ | — | — | — | Dense, brittle bones. $Ca^{2+}$ ↓ in severe, malignant disease |
| **Paget disease of bone** | — | — | ↑ | — | Abnormal "mosaic" bone architecture |
| **Osteitis fibrosa cystica** Primary hyperparathyroidism | ↑ | ↓ | ↑ | ↑ | "Brown tumors" due to fibrous replacement of bone, subperiosteal thinning<br>Idiopathic or parathyroid hyperplasia, adenoma, carcinoma |
| Secondary hyperparathyroidism | ↓ | ↑ | ↑ | ↑ | Often as compensation for CKD (↓ $PO_4^{3-}$ excretion and production of activated vitamin D) |
| **Osteomalacia/rickets** | ↓ | ↓ | ↑ | ↑ | Soft bones; vitamin D deficiency also causes 2° hyperparathyroidism |
| **Hypervitaminosis D** | ↑ | ↑ | — | ↓ | Caused by oversupplementation or granulomatous disease (eg, sarcoidosis) |

↑ ↓ = 1° change.

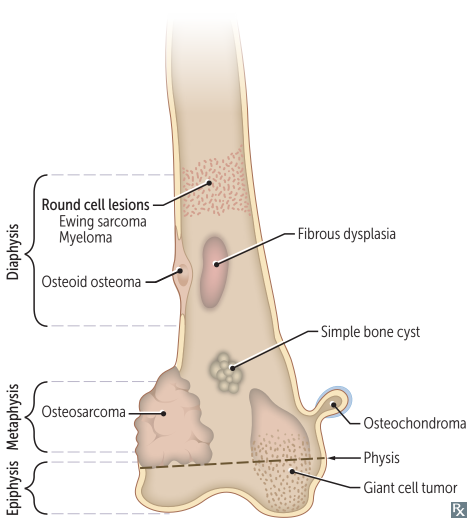
---

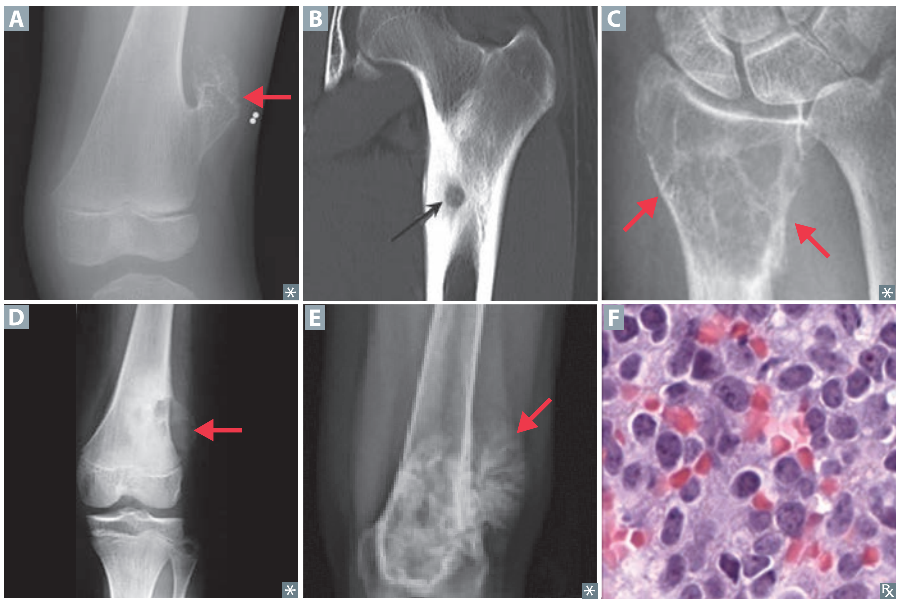
**Primary bone tumors** Metastatic disease is more common than 1° bone tumors. Benign bone tumors that start with **o** are more common in b**o**ys.

| TUMOR TYPE | EPIDEMIOLOGY | LOCATION | CHARACTERISTICS |
|---|---|---|---|
| Benign tumors | | | |
| **Osteochondroma** | Most common benign bone tumor<br>Males < 25 years old | Metaphysis of long bones | Lateral bony projection of growth plate (continuous with marrow space) covered by cartilaginous cap A<br>Rarely transforms to chondrosarcoma |
| **Osteoma** | Middle age | Surface of facial bones | Associated with Gardner syndrome |
| **Osteoid osteoma** | Adults < 25 years old<br>Males > females | Cortex of long bones | Presents as bone pain (worse at night) that is relieved by NSAIDs<br>Bony mass (< 2 cm) with radiolucent osteoid core B |
| **Osteoblastoma** | Males > females | Vertebrae | Similar histology to osteoid osteoma<br>Larger size (> 2 cm), pain unresponsive to NSAIDs |
| **Chondroma** | | Medulla of small bones of hand and feet | Benign tumor of cartilage |
| **Giant cell tumor** | 20–40 years old | Epiphysis of long bones (often in knee region) | Locally aggressive benign tumor<br>Neoplastic mononuclear cells that express RANKL and reactive multinucleated giant (osteoclast-like) cells. "Osteoclastoma"<br>"Soap bubble" appearance on x-ray C |

## Primary bone tumors *(continued)*

| TUMOR TYPE | EPIDEMIOLOGY | LOCATION | CHARACTERISTICS |
|---|---|---|---|
| **Malignant tumors** | | | |
| **Osteosarcoma (osteogenic sarcoma)** | Accounts for 20% of 1° bone cancers.<br>Peak incidence of 1° tumor in males < 20 years.<br>Less common in elderly; usually 2° to predisposing factors, such as Paget disease of bone, bone infarcts, radiation, familial retinoblastoma, Li-Fraumeni syndrome. | Metaphysis of long bones (often in knee region). | Pleomorphic osteoid-producing cells (malignant osteoblasts).<br>Presents as painful enlarging mass or pathologic fractures.<br>Codman triangle D (from elevation of periosteum) or sunburst pattern on x-ray E (think of an osteocod [bone fish] swimming in the sun).<br>Aggressive. 1° usually responsive to treatment (surgery, chemotherapy), poor prognosis for 2°. |
| **Chondrosarcoma** | | Medulla of pelvis, proximal femur and humerus. | Tumor of malignant chondrocytes. |
| **Ewing sarcoma** | Most common in White patients.<br>Generally males < 15 years old. | Diaphysis of long bones (especially femur), pelvic flat bones. | Anaplastic small blue cells of neuroectodermal origin (resemble lymphocytes) F.<br>Differentiate from conditions with similar morphology (eg, lymphoma, chronic osteomyelitis) by testing for t(11;22) (fusion protein EWS-FLI1).<br>"Onion skin" periosteal reaction in bone.<br>Aggressive with early metastases, but responsive to chemotherapy.<br>11 + 22 = 33 (Patrick Ewing's jersey number). |

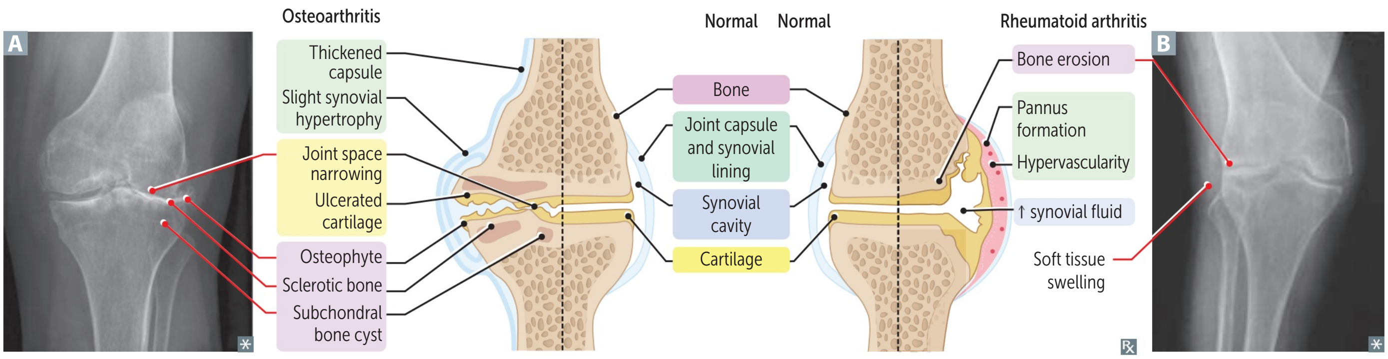


## Osteoarthritis vs rheumatoid arthritis

| | Osteoarthritis A | Rheumatoid arthritis B |
|---|---|---|
| PATHOGENESIS | Mechanical—wear and tear destroys articular cartilage (degenerative joint disorder) → inflammation with inadequate repair. Chondrocytes mediate degradation and inadequate repair. | Autoimmune—inflammation C induces formation of pannus (proliferative granulation tissue), which erodes articular cartilage and bone. |
| PREDISPOSING FACTORS | Age, female, obesity, joint trauma. | Female, HLA-DR4 (4-walled "**rheum**"), tobacco smoking. ⊕ rheumatoid factor (IgM antibody that targets IgG Fc region; in 80%), anti-cyclic citrullinated peptide antibody (more specific). |
| PRESENTATION | Pain in weight-bearing joints after use (eg, at the end of the day), improving with rest. Asymmetric joint involvement. Knee cartilage loss begins medially ("bowlegged"). No systemic symptoms. | Pain, swelling, and morning stiffness lasting > 1 hour, improving with use. Symmetric joint involvement. Systemic symptoms (fever, fatigue, weight loss). Extraarticular manifestations common.* |
| JOINT FINDINGS | Osteophytes (bone spurs), joint space narrowing, subchondral sclerosis and cysts. Synovial fluid noninflammatory (WBC < $2000/mm^3$). Development of Heberden nodes D (at DIP) and Bouchard nodes E (at PIP), and 1st CMC; not MCP. | Erosions, juxta-articular osteopenia, soft tissue swelling, subchondral cysts, joint space narrowing. Deformities: cervical subluxation, ulnar finger deviation, swan neck F, boutonniere G. Involves MCP, PIP, wrist; not DIP or 1st CMC. |
| TREATMENT | Activity modification, acetaminophen, NSAIDs, intra-articular glucocorticoids. | NSAIDs, glucocorticoids, disease-modifying agents (eg, methotrexate, sulfasalazine), biologic agents (eg, TNF-α inhibitors). |

*Extraarticular manifestations include rheumatoid nodules (fibrinoid necrosis with palisading histiocytes) in subcutaneous tissue and lung (+ pneumoconiosis → Caplan syndrome), interstitial lung disease, pleuritis, pericarditis, anemia of chronic disease, neutropenia + splenomegaly (Felty syndrome), AA amyloidosis, Sjögren syndrome, scleritis, carpal tunnel syndrome.




## Gout

**FINDINGS**

Acute inflammatory monoarthritis caused by precipitation of monosodium urate crystals in joints A. Risk factors: male sex, hypertension, obesity, diabetes, dyslipidemia, alcohol use. Strongest risk factor is hyperuricemia, which can be caused by:

- Underexcretion of uric acid (90% of patients)—largely idiopathic, potentiated by renal failure; can be exacerbated by certain medications (eg, thiazide diuretics).
- Overproduction of uric acid (10% of patients)—Lesch-Nyhan syndrome, PRPP excess, $\uparrow$ cell turnover (eg, tumor lysis syndrome), von Gierke disease.

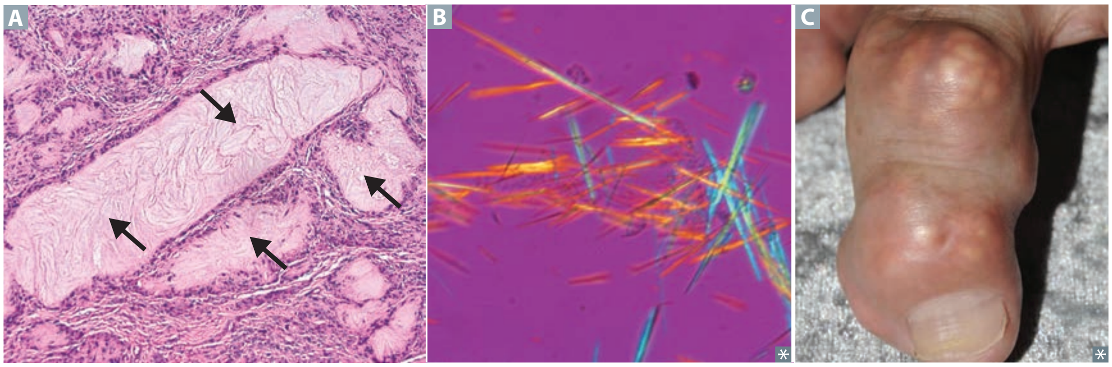
Crystals are needle shaped and $\ominus$ birefringent under polarized light (yellow under parallel light, blue under perpendicular light B). Serum uric acid levels may be normal during an acute attack.

**SYMPTOMS**

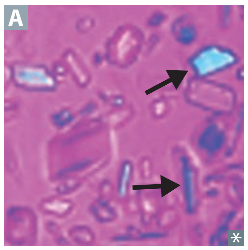
Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of big toe (podagra). Tophus formation C (often on external ear, olecranon bursa, or Achilles tendon). Acute attack tends to occur after a large meal with foods rich in purines (eg, red meat, seafood), trauma, surgery, dehydration, diuresis, or alcohol consumption (alcohol metabolites compete for same excretion sites in kidney as uric acid $\rightarrow$ $\downarrow$ uric acid secretion and subsequent buildup in blood).

**TREATMENT**

Acute: NSAIDs (eg, indomethacin), glucocorticoids, colchicine.
Chronic (preventive): xanthine oxidase inhibitors (eg, allopurinol, febuxostat).



## Calcium pyrophosphate deposition disease



Previously called pseudogout. Deposition of calcium pyrophosphate crystals within the joint space. Occurs in patients > 50 years old; both sexes affected equally. Usually idiopathic, sometimes associated with hemochromatosis, hyperparathyroidism, joint trauma.

Pain and swelling with acute inflammation (pseudogout) and/or chronic degeneration (pseudo-osteoarthritis). Most commonly affected joint is the knee.

Chondrocalcinosis (cartilage calcification) on x-ray.

Crystals are rhomboid and weakly $\oplus$ birefringent under polarized light (blue when parallel to light) A.

Acute treatment: NSAIDs, colchicine, glucocorticoids.

Prophylaxis: colchicine.

The **blue P**'s—**blue** (when **p**arallel), **p**ositive birefringence, calcium **p**yrophosphate, **p**seudogout

**Systemic juvenile idiopathic arthritis**

Systemic arthritis seen in < 16 year olds. Usually presents with daily spiking fevers, salmon-pink macular rash, arthritis (commonly 2+ joints). Associated with anterior uveitis. Frequently presents with leukocytosis, thrombocytosis, anemia, ↑ ESR, ↑ CRP. Treatment: NSAIDs, steroids, methotrexate, TNF inhibitors.

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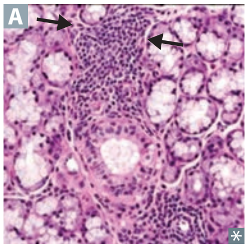
**Sjögren syndrome**


A


B

Autoimmune disorder characterized by destruction of exocrine glands (especially lacrimal and salivary) by lymphocytic infiltrates A. Predominantly affects females 40–60 years old.

Findings:
- Inflammatory joint pain
- Keratoconjunctivitis sicca (↓ tear production and subsequent corneal damage)
- Xerostomia (↓ saliva production) → mucosal atrophy, fissuring of the tongue B
- Presence of antinuclear antibodies, rheumatoid factor (can be positive in the absence of rheumatoid arthritis), antiribonucleoprotein antibodies: SS-A (anti-Ro) and/or SS-B (anti-La)
- Bilateral parotid enlargement

Anti-SSA and anti-SSB may also be seen in SLE.

A common 1° disorder or a 2° syndrome associated with other autoimmune disorders (eg, rheumatoid arthritis, SLE, systemic sclerosis).

Complications: dental caries; mucosa-associated lymphoid tissue (MALT) lymphoma (may present as parotid enlargement); ↑ risk of giving birth to baby with neonatal lupus.

Focal lymphocytic sialadenitis on labial salivary gland biopsy can confirm diagnosis.

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**Septic arthritis**


A

*S aureus*, *Streptococcus*, and *Neisseria gonorrhoeae* are common causes. Affected joint is swollen A, red, and painful. Synovial fluid purulent (WBC > 50,000/mm$^3$).

Disseminated gonococcal infection—STI that presents as either purulent arthritis (eg, knee) or triad of polyarthralgia, tenosynovitis (eg, hand), dermatitis (eg, pustules).

| | | |
|---|---|---|
| **Seronegative spondyloarthritis** | Arthritis without rheumatoid factor (no anti-IgG antibody). Strong association with HLA-B27 (MHC class I serotype). Subtypes (**PAIR**) share variable occurrence of inflammatory back pain (associated with morning stiffness, improves with exercise), peripheral arthritis, enthesitis (inflamed insertion sites of tendons, eg, Achilles), dactylitis ("sausage fingers"), uveitis. | |
| **Psoriatic arthritis** | Associated with skin psoriasis and nail lesions. Asymmetric and patchy involvement A. Dactylitis and "pencil-in-cup" deformity of DIP on x-ray B. | Seen in fewer than ⅓ of patients with psoriasis. |
| **Ankylosing spondylitis** | Symmetric involvement of spine and sacroiliac joints → ankylosis (joint fusion), uveitis, aortic regurgitation. | Bamboo spine (vertebral fusion) C. Costovertebral and costosternal ankylosis may cause restrictive lung disease. Monitor degree of reduced chest wall expansion to assess disease severity. More common in males. |
| **Inflammatory bowel disease** | Crohn disease and ulcerative colitis are often associated with spondyloarthritis. | |
| **Reactive arthritis** | Classic triad: ▪ **Conjunctivitis** ▪ **Urethritis** ▪ **Arthritis** | "Can't **see**, can't **pee**, can't **bend my knee**." Associated with infections by *Shigella*, *Campylobacter*, *E coli*, *Salmonella*, *Chlamydia*, *Yersinia*. "**S**he **C**aught **E**very **S**tudent **C**heating **Y**esterday and over**react**ed." |

**Systemic lupus erythematosus**

Systemic, remitting, and relapsing autoimmune disease. Organ damage primarily due to a type III hypersensitivity reaction and, to a lesser degree, a type II hypersensitivity reaction. Associated with deficiency of early complement proteins (eg, C1q, C4, C2) → ↓ clearance of immune complexes. Classic presentation: rash, joint pain, and fever in a female of reproductive age. ↑ prevalence in Black, Caribbean, Asian, and Hispanic populations.

A

B

**L**ibman-**S**acks **E**ndocarditis—nonbacterial, verrucous thrombi usually on mitral or aortic valve and can be present on either surface of the valve (but usually on undersurface). **LSE** in **SLE**.

Lupus nephritis (glomerular deposition of DNA-anti-DNA immune complexes) can be nephritic or nephrotic (causing hematuria or proteinuria). Most common and severe type is diffuse proliferative.

Common causes of death in SLE: **i**nfections, **c**ardiovascular disease (accelerated CAD), **k**idney disease (most common). **I**mmune **c**omplexes **k**ill.

In an anti-SSA ⊕ pregnant patient, ↑ risk of newborn developing neonatal lupus → congenital heart block, periorbital/diffuse rash, transaminitis, and cytopenias at birth.

**RASH OR PAIN**:
- **R**ash (malar A or discoid B)
- **A**rthritis (nonerosive)
- **S**erositis (eg, pleuritis, pericarditis)
- **H**ematologic disorders (eg, cytopenias)
- **O**ral/nasopharyngeal ulcers (usually painless)
- **R**enal disease
- **P**hotosensitivity
- **A**ntinuclear antibodies
- **I**mmunologic disorder (anti-dsDNA, anti-Sm, antiphospholipid)
- **N**eurologic disorders (eg, seizures, psychosis)

**Mixed connective tissue disease**

Features of SLE, systemic sclerosis, and/or polymyositis. Associated with anti-U1 RNP antibodies (speckled ANA).

**Antiphospholipid syndrome**

1° or 2° autoimmune disorder (most commonly in SLE).

Diagnosed based on clinical criteria including history of thrombosis (arterial or venous) or spontaneous abortion along with laboratory findings of lupus anticoagulant, anticardiolipin, anti-$\beta_2$ glycoprotein I antibodies.

Treatment: systemic anticoagulation.

Anticardiolipin antibodies can cause false-positive VDRL/RPR.

Lupus anticoagulant can cause prolonged PTT that is not corrected by the addition of normal platelet-free plasma.

## Polymyalgia rheumatica

| | |
|---|---|
| SYMPTOMS | Pain and stiffness in proximal muscles (eg, shoulders, hips), often with fever, malaise, weight loss. Does not cause muscular weakness. More common in females > 50 years old; associated with giant cell (temporal) arteritis. |
| FINDINGS | ↑ ESR, ↑ CRP, normal CK. |
| TREATMENT | Rapid response to low-dose corticosteroids. |

**Fibromyalgia**

Most common in females 20–50 years old. Chronic, widespread musculoskeletal pain associated with "tender points," stiffness, paresthesias, poor sleep, fatigue, cognitive disturbance ("fibro fog"). Treatment: regular exercise, antidepressants (TCAs, SNRIs), neuropathic pain agents (eg, gabapentin).

| | |
|---|---|
| **Polymyositis/ dermatomyositis** | Nonspecific: ⊕ ANA, ↑ CK. Specific: ⊕ anti-Jo-1 (histidyl-tRNA synthetase), ⊕ anti-SRP (signal recognition particle), ⊕ anti-Mi-2 (helicase). |
| **Polymyositis** | Progressive symmetric proximal muscle weakness, characterized by endomysial inflammation with CD8+ T cells. Most often involves shoulders. |
| **Dermatomyositis** | Clinically similar to polymyositis, but also involves Gottron papules A, photodistributed facial erythema (eg, heliotrope [violaceous] edema of the eyelids B), "shawl and face" rash C, darkening and thickening of fingertips and sides resulting in irregular, "dirty"-appearing marks. ↑ risk of occult malignancy. Perimysial inflammation and atrophy with CD4+ T cells. |


**Myositis ossificans**

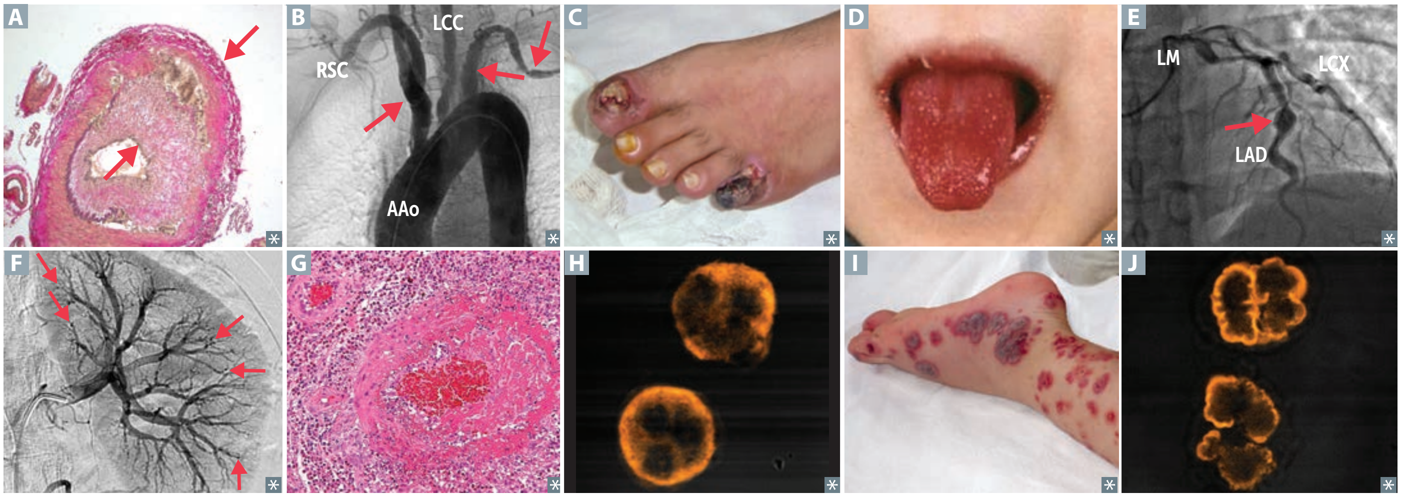
Heterotopic ossification involving skeletal muscle (eg, quadriceps). Associated with blunt muscle trauma. Presents as painful soft tissue mass. Imaging shows eggshell calcification. Histology shows metaplastic bone surrounding area of fibroblastic proliferation. Benign, but may be mistaken for sarcoma.

## Vasculitides

| | EPIDEMIOLOGY/PRESENTATION | NOTES |
|---|---|---|
| **Large-vessel vasculitis** | | |
| **Giant cell (temporal) arteritis** | Females > 50 years old.<br>Unilateral headache, possible temporal artery tenderness, jaw claudication.<br>May lead to irreversible blindness due to anterior ischemic optic neuropathy.<br>Associated with polymyalgia rheumatica. | Most commonly affects branches of carotid artery.<br>Focal granulomatous inflammation A.<br>↑ ESR.<br>Treat with high-dose corticosteroids prior to temporal artery biopsy to prevent blindness. |
| **Takayasu arteritis** | Usually Asian females < 40 years old.<br>"Pulseless disease" (weak upper extremity pulses), fever, night sweats, arthritis, myalgias, skin nodules, ocular disturbances. | Granulomatous thickening and narrowing of aortic arch and proximal great vessels B.<br>↑ ESR.<br>Treatment: corticosteroids. |
| **Medium-vessel vasculitis** | | |
| **Buerger disease (thromboangiitis obliterans)** | Heavy tobacco smoking history, males < 40 years old.<br>Intermittent claudication. May lead to gangrene C, autoamputation of digits, superficial nodular phlebitis.<br>Raynaud phenomenon is often present. | Segmental thrombosing vasculitis with vein and nerve involvement.<br>Treatment: smoking cessation. |
| **Kawasaki disease (mucocutaneous lymph node syndrome)** | Usually Asian children < 4 years old.<br>Conjunctival injection, Rash (polymorphous → desquamating), Adenopathy (cervical), Strawberry tongue (oral mucositis) D, Hand-foot changes (edema, erythema), fever. | CRASH and burn on a Kawasaki.<br>May develop coronary artery aneurysms E; thrombosis or rupture can cause death.<br>Treatment: IV immunoglobulin and aspirin. |
| **Polyarteritis nodosa** | Usually middle-aged males.<br>Hepatitis B seropositivity in 30% of patients.<br>Fever, weight loss, malaise, headache.<br>GI: abdominal pain, melena.<br>Hypertension, neurologic dysfunction, cutaneous eruptions, renal damage. | Typically involves renal and visceral vessels, not pulmonary arteries.<br>Different stages of transmural inflammation with fibrinoid necrosis.<br>Innumerable renal microaneurysms F and spasms on arteriogram (string of pearls appearance).<br>Treatment: corticosteroids, cyclophosphamide. |
| **Small-vessel vasculitis** | | |
| **Behçet syndrome** | ↑ incidence in people of Turkish and eastern Mediterranean descent.<br>Recurrent aphthous ulcers, genital ulcerations, uveitis, erythema nodosum. Can be precipitated by HSV or parvovirus. Flares last 1–4 weeks. | Immune complex vasculitis.<br>Associated with HLA-B51. |
| **Cutaneous small-vessel vasculitis** | Occurs 7-10 days after certain medications (penicillin, cephalosporins, phenytoin, allopurinol) or infections (eg, HCV, HIV).<br>Palpable purpura, no visceral involvement. | Immune complex–mediated leukocytoclastic vasculitis; late involvement indicates systemic vasculitis. |

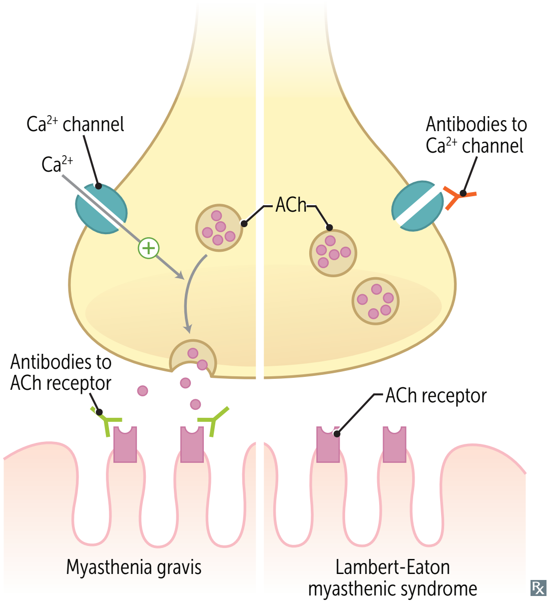
## Vasculitides *(continued)*

| | EPIDEMIOLOGY/PRESENTATION | NOTES |
|---|---|---|
| Small-vessel vasculitis *(continued)* | | |
| **Eosinophilic granulomatosis with polyangiitis** | Asthma, sinusitis, skin nodules or purpura, peripheral neuropathy (eg, wrist/foot drop).<br>Can also involve heart, GI, kidneys (pauci-immune glomerulonephritis). | Formerly called Churg-Strauss syndrome.<br>Granulomatous, necrotizing vasculitis with eosinophilia G.<br>MPO-ANCA/p-ANCA, ↑ IgE level. |
| **Granulomatosis with polyangiitis** | Upper respiratory tract: perforation of nasal septum, chronic sinusitis, otitis media, mastoiditis.<br>Lower respiratory tract: hemoptysis, cough, dyspnea.<br>Renal: hematuria, red cell casts. | Triad:<br>▪ Focal necrotizing vasculitis<br>▪ Necrotizing granulomas in lung and upper airway<br>▪ Necrotizing glomerulonephritis<br>PR3-ANCA/c-ANCA H (anti-proteinase 3).<br>CXR: large nodular densities.<br>Treatment: corticosteroids in combination with rituximab or cyclophosphamide. |
| **Immunoglobulin A vasculitis** | Most common childhood systemic vasculitis.<br>Often follows URI.<br>Classic triad of **H**enoch-**S**chönlein **p**urpura<br>▪ **H**inge pain (arthralgias)<br>▪ **S**tomach pain (abdominal pain associated with intussusception)<br>▪ **P**alpable purpura on buttocks/legs I | Formerly called Henoch-Schönlein purpura.<br>Vasculitis 2° to IgA immune complex deposition.<br>Associated with IgA nephropathy (Berger disease).<br>Treatment: supportive care, possibly corticosteroids. |
| **Microscopic polyangiitis** | Necrotizing vasculitis commonly involving lung, kidneys, and skin with pauci-immune glomerulonephritis and palpable purpura.<br>Presentation similar to granulomatosis with polyangiitis but without nasopharyngeal involvement. | No granulomas.<br>MPO-ANCA/p-ANCA J (anti-myeloperoxidase).<br>Treatment: cyclophosphamide, corticosteroids. |
| **Mixed cryoglobulinemia** | Often due to viral infections, especially H**C**V.<br>Triad of palpable purpura, weakness, arthralgias.<br>May also have peripheral neuropathy and renal disease (eg, glomerulonephritis). | **C**ryoglobulins are immunoglobulins that precipitate in the **C**old.<br>Vasculitis due to mixed IgG and IgM immune complex deposition. |

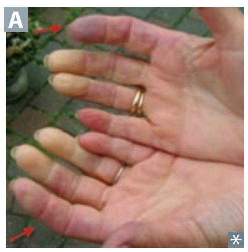


## Neuromuscular junction diseases

| | Myasthenia gravis | Lambert-Eaton myasthenic syndrome |
|---|---|---|
| FREQUENCY | Most common NMJ disorder | Uncommon |
| PATHOPHYSIOLOGY | Autoantibodies to postsynaptic ACh receptor | Autoantibodies to presynaptic $Ca^{2+}$ channel → ↓ ACh release |
| CLINICAL | Fatigable muscle weakness—ptosis; diplopia; proximal weakness; respiratory muscle involvement → dyspnea; bulbar muscle involvement → dysphagia, difficulty chewing<br>Spared reflexes<br>Worsens with muscle use | Proximal muscle weakness, autonomic symptoms (dry mouth, constipation, impotence)<br>Hyporeflexia<br>Improves with muscle use |
| ASSOCIATED WITH | Thymoma, thymic hyperplasia | Small cell lung cancer |
| AChE INHIBITOR ADMINISTRATION | Reverses symptoms (pyridostigmine for treatment) | Minimal effect |




**Raynaud phenomenon**




↓ blood flow to skin due to arteriolar (small vessel) vasospasm in response to cold or stress: color change from white (ischemia) to blue (hypoxia) to red (reperfusion). Most often in the fingers A and toes. Called Raynaud disease when 1° (idiopathic), Raynaud syndrome when 2° to a disease process such as mixed connective tissue disease, SLE, or CREST syndrome (limited form of systemic sclerosis). Digital ulceration (critical ischemia) seen in 2° Raynaud syndrome. Treat with calcium channel blockers.

**Scleroderma**

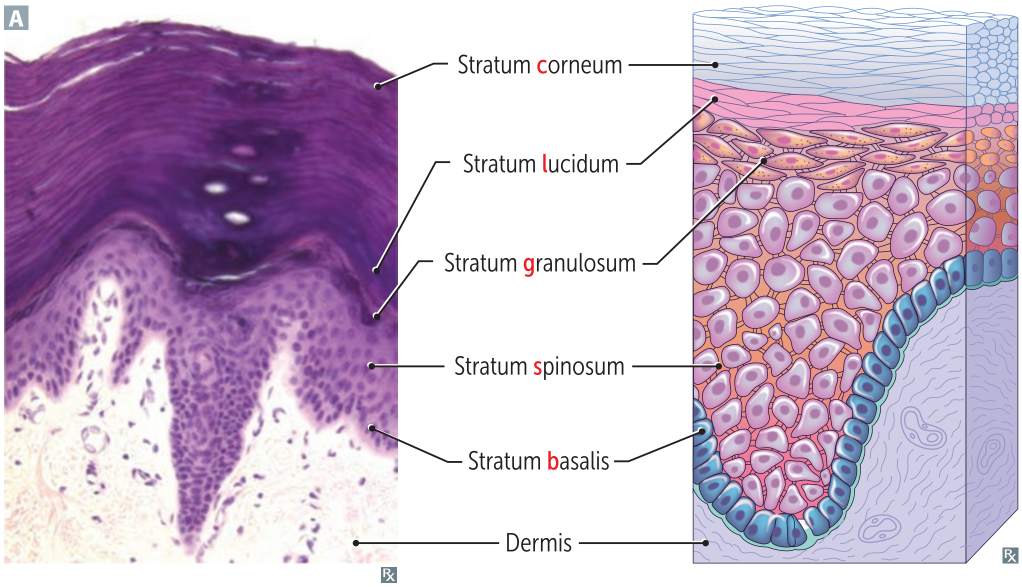
Systemic sclerosis. Triad of autoimmunity, noninflammatory vasculopathy, and collagen deposition with fibrosis. Commonly sclerosis of skin, manifesting as puffy, taut skin A without wrinkles, fingertip pitting B. Can involve other systems, eg, renal (scleroderma renal crisis; treat with ACE inhibitors), pulmonary (interstitial fibrosis, pulmonary HTN), GI (esophageal dysmotility and reflux), cardiovascular. 75% female. 2 major types:

- **Diffuse scleroderma**—widespread skin involvement, rapid progression, early visceral involvement. Associated with anti-Scl-70 antibody (anti-DNA topoisomerase-I antibody) and anti-RNA polymerase III.
- **Limited scleroderma**—limited skin involvement confined to fingers and face. Also with CREST syndrome: Calcinosis cutis C, anti-Centromere antibody, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia. More benign clinical course.

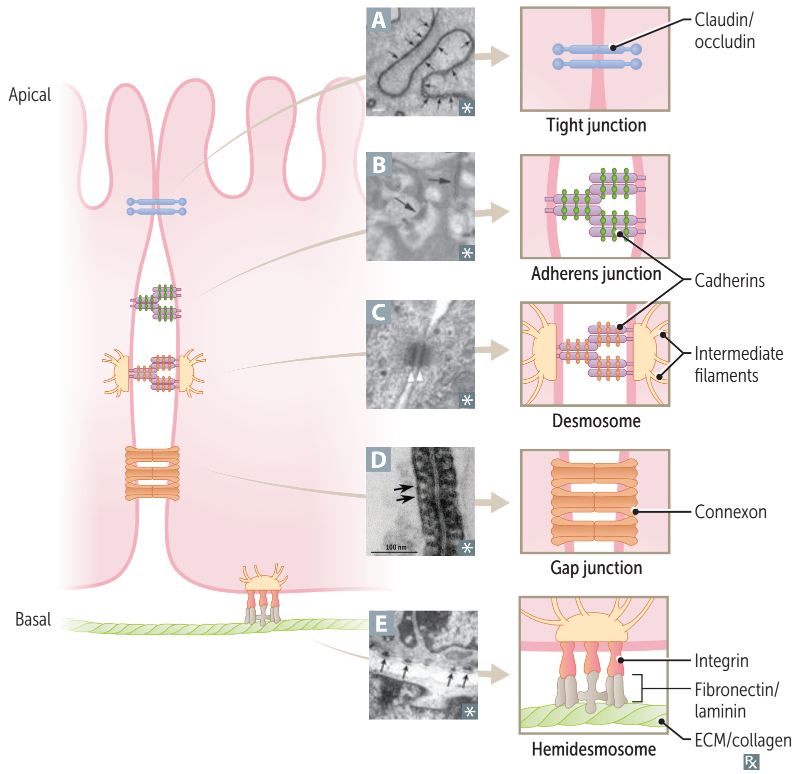

## ▶ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—DERMATOLOGY

**Skin layers**

Skin has 3 layers: epidermis, dermis, subcutaneous fat (hypodermis, subcutis).
Epidermal layers: come, let's get sunburned.



## Epithelial cell junctions




Tight junctions (zonula occludens) A–prevents paracellular movement of solutes; composed of claudins and occludins.

Adherens junction (belt desmosome, zonula adherens) B–forms "belt" connecting actin cytoskeletons of adjacent cells with **cad**herins (**Ca**$^{2+}$-dependent **ad**hesion proteins). Loss of E-cadherin promotes metastasis.

Desmosome (spot desmosome, macula adherens) C–structural support via intermediate filament interactions. Autoantibodies to desmoglein 1 and/or 3 → pemphigus vulgaris.

Gap junction D–channel proteins called connexons permit electrical and chemical communication between cells.

Hemidesmosome E–connects keratin in basal cells to underlying basement membrane. Autoantibodies → **bullo**us pemphigoid. (Hemidesmosomes are down "**bullo**w.")

**Integri**ns–membrane proteins that maintain **integri**ty of basolateral membrane by binding to collagen, laminin, and fibronectin in basement membrane.

## Dermatologic macroscopic terms

| LESION | CHARACTERISTICS | EXAMPLES |
|---|---|---|
| **Macule** | Flat lesion with well-circumscribed change in skin color < 1 cm | Freckle (ephelide), labial macule A |
| **Patch** | Macule > 1 cm | Large birthmark (congenital nevus) B |
| **Papule** | Elevated solid skin lesion < 1 cm | Mole (nevus) C, acne |
| **Plaque** | Papule > 1 cm | Psoriasis D |
| **Vesicle** | Small fluid-containing blister < 1 cm | Chickenpox (varicella), shingles (zoster) E |
| **Bulla** | Large fluid-containing blister > 1 cm | Bullous pemphigoid F |
| **Pustule** | Vesicle containing pus | Pustular psoriasis G |
| **Wheal** | Transient smooth papule or plaque | Hives (urticaria) H |
| **Scale** | Flaking off of stratum corneum | Eczema, psoriasis, SCC I |
| **Crust** | Dry exudate | Impetigo J |


## Dermatologic microscopic terms

| LESION | CHARACTERISTICS | EXAMPLES |
|---|---|---|
| **Dyskeratosis** | Abnormal premature keratinization | Squamous cell carcinoma |
| **Hyperkeratosis** | ↑ thickness of stratum corneum | Psoriasis, calluses |
| **Parakeratosis** | Retention of nuclei in stratum corneum | Psoriasis, actinic keratosis |
| **Hypergranulosis** | ↑ thickness of stratum granulosum | Lichen planus |
| **Spongiosis** | Epidermal accumulation of edematous fluid in intercellular spaces | Eczematous dermatitis |
| **Acantholysis** | Separation of epidermal cells | Pemphigus vulgaris |
| **Acanthosis** | Epidermal hyperplasia (↑ spinosum) | Acanthosis nigricans, psoriasis |

## Pigmented skin disorders

| | |
|---|---|
| **Albinism** | Normal melanocyte number with ↓ melanin production A due to ↓ tyrosinase activity or defective tyrosine transport. ↑ risk of skin cancer. |
| **Melasma (chloasma)** | Acquired hyperpigmentation associated with pregnancy ("mask of pregnancy" B) or OCP use. More common in pregnant patients with darker skin tones. |
| **Vitiligo** | Irregular patches of complete depigmentation C. Caused by destruction of melanocytes (believed to be autoimmune). Associated with other autoimmune disorders. |


## Seborrheic dermatitis

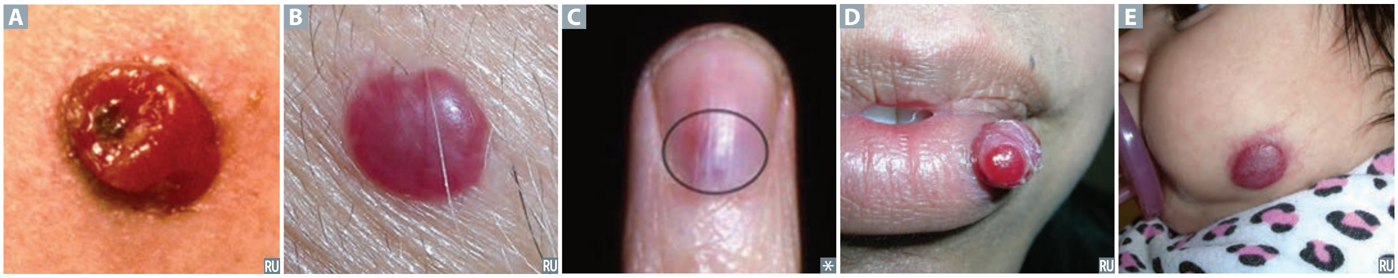

Erythematous, well-demarcated plaques A with greasy yellow scales in areas rich in sebaceous glands, such as scalp, face, and periocular region. Common in both infants (cradle cap) and adults, associated with Parkinson disease. Sebaceous glands are not inflamed, but play a role in disease development. Possibly associated with *Malassezia* spp. Treatment: topical antifungals and corticosteroids.

## Common skin disorders

| | |
|---|---|
| **Acne** | Multifactorial etiology—$\uparrow$ sebum/androgen production, abnormal keratinocyte desquamation, *Cutibacterium acnes* colonization of the pilosebaceous unit (comedones), and inflammation (papules/pustules A, nodules, cysts). Treatment: retinoids, benzoyl peroxide, and antibiotics. |
| **Atopic dermatitis (eczema)** | Type I hypersensitivity reaction. Pruritic eruption, commonly on skin flexures. Associated with other atopic diseases (asthma, allergic rhinitis, food allergies); $\uparrow$ serum IgE. Mutations in filaggrin gene predispose (via skin barrier dysfunction). Often appears on face in infancy B and then in antecubital fossa C in children and adults. |
| **Allergic contact dermatitis** | Type IV hypersensitivity reaction secondary to contact allergen (eg, nickel D, poison ivy, neomycin E). |
| **Melanocytic nevus** | Common mole. Benign, but melanoma can arise in congenital or atypical moles. Intradermal nevi are papular F. Junctional nevi are flat macules G. |
| **Pseudofolliculitis barbae** | Foreign body inflammatory facial skin disorder characterized by firm, hyperpigmented papules and pustules that are painful and pruritic. Located on cheeks, jawline, and neck. Commonly occurs as a result of shaving ("razor bumps"), primarily affects Black males. |
| **Psoriasis** | Papules and plaques with silvery scaling H, especially on knees and elbows. Acanthosis with parakeratotic scaling (nuclei still in stratum corneum), Munro microabscesses. $\uparrow$ stratum spinosum, $\downarrow$ stratum granulosum. Auspitz sign (I)—pinpoint bleeding spots from exposure of dermal papillae when scales are scraped off. Associated with nail pitting and psoriatic arthritis. |
| **Rosacea** | Inflammatory facial skin disorder characterized by erythematous papules and pustules J, but no comedones. May be associated with facial flushing in response to external stimuli (eg, alcohol, heat). Complications include ocular involvement, rhinophyma (bulbous deformation of nose). |
| **Seborrheic keratosis** | Flat, greasy, pigmented squamous epithelial proliferation of immature keratinocytes with keratin-filled cysts (horn cysts) K. Looks "stuck on." Lesions occur on head, trunk, and extremities. Common benign neoplasm of older persons. Leser-Trélat sign L—rapid onset of multiple seborrheic keratoses, indicates possible malignancy (eg, GI adenocarcinoma). |
| **Verrucae** | Warts; caused by low-risk HPV strains. Soft, tan-colored, cauliflower-like papules M. Epidermal hyperplasia, hyperkeratosis, koilocytosis. Condyloma acuminatum on anus or genitals N. |
| **Urticaria** | Hives. Pruritic wheals that form after mast cell degranulation O. Characterized by superficial dermal edema and lymphatic channel dilation. |

## Vascular tumors of skin

| | |
|---|---|
| **Angiosarcoma** | Rare blood vessel malignancy typically occurring in the head, neck, and breast areas. Usually in elderly, on sun-exposed areas. Associated with radiation therapy and chronic postmastectomy lymphedema. Hepatic angiosarcoma associated with vinyl chloride and arsenic exposures. Very aggressive and difficult to resect due to delay in diagnosis. |
| **Bacillary angiomatosis** | Benign capillary skin papules A found in patients with AIDS. Caused by *Bartonella* infections. Frequently mistaken for Kaposi sarcoma, but has neutrophilic infiltrate. |
| **Cherry hemangioma** | Benign capillary hemangioma B commonly appearing in middle-aged adults. Does not regress. Frequency ↑ with age. |
| **Glomus tumor** | Benign, painful, red-blue tumor, commonly under fingernails C. Arises from modified smooth muscle cells of the thermoregulatory glomus body. |
| **Kaposi sarcoma** | Endothelial malignancy most commonly affecting the skin, mouth, GI tract, respiratory tract. Classically seen in older Eastern European males, patients with AIDS, and organ transplant patients. Associated with HHV-8 and HIV. Lymphocytic infiltrate, unlike bacillary angiomatosis. |
| **Pyogenic granuloma** | Polypoid lobulated capillary hemangioma D that can ulcerate and bleed. Associated with trauma and pregnancy. |
| **Strawberry hemangioma** | Benign capillary hemangioma of infancy E. Appears in first few weeks of life (1/200 births); grows rapidly and regresses spontaneously by 5–8 years old. |

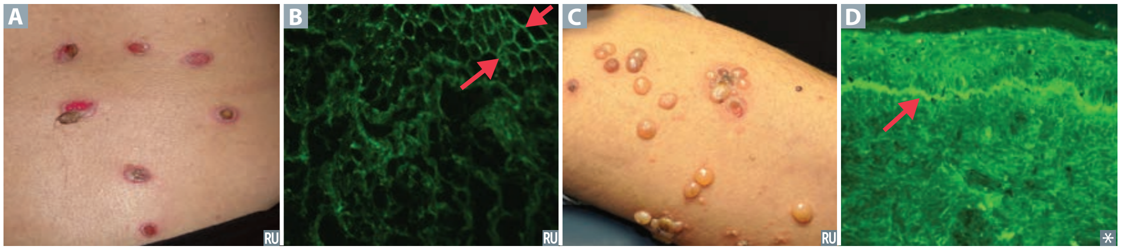


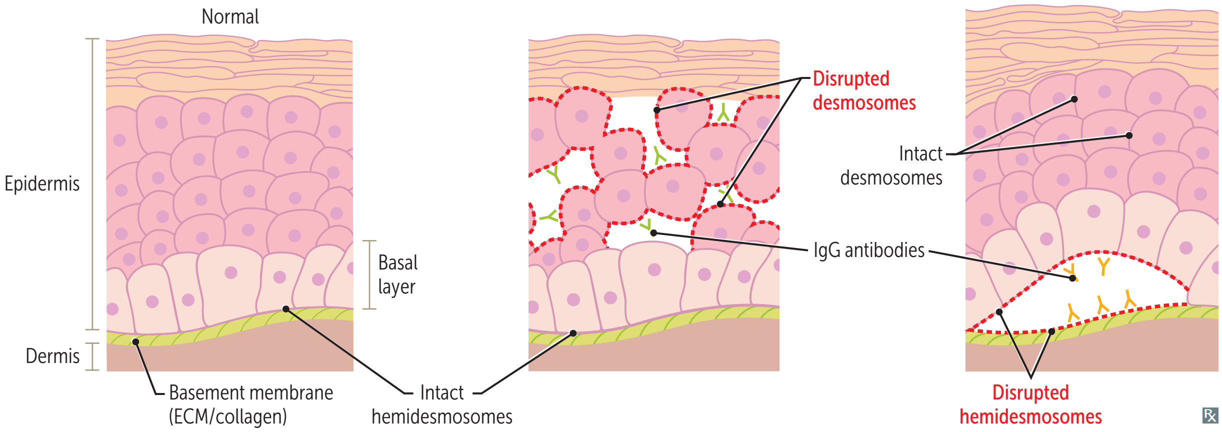
## Skin infections

| | |
|---|---|
| **Bacterial infections** | |
| **Impetigo** | Skin infection involving superficial epidermis. Usually from *S aureus* or *S pyogenes*. Highly contagious. Honey-colored crusting A.<br>Bullous impetigo B has bullae and is usually caused by *S aureus*. |
| **Erysipelas** | Infection involving upper dermis and superficial lymphatics, usually from *S pyogenes*. Presents with well-defined, raised demarcation between infected and normal skin C. |
| **Cellulitis** | Acute, painful, spreading infection of deeper dermis and subcutaneous tissues. Usually from *S pyogenes* or *S aureus*. Often starts with a break in skin from trauma or another infection D. |
| **Abscess** | Collection of pus from a walled-off infection within deeper layers of skin E. Offending organism is almost always *S aureus*. |
| **Necrotizing fasciitis** | Deeper tissue injury, usually from anaerobic bacteria or *S pyogenes*. Pain may be out of proportion to exam findings. Results in crepitus from methane and $CO_2$ production. "Flesh-eating bacteria." Causes bullae and skin necrosis → violaceous color of bullae, surrounding skin F. Surgical emergency. |
| **Staphylococcal scalded skin syndrome** | Exotoxin destroys keratinocyte attachments in stratum granulosum only (vs toxic epidermal necrolysis, which destroys epidermal-dermal junction). Characterized by fever and generalized erythematous rash with sloughing of the upper layers of the epidermis G that heals completely. ⊕ Nikolsky sign (separation of epidermis upon manual stroking of skin). Commonly seen in newborns and children/adults with renal insufficiency. |
| **Viral infections** | |
| **Herpes** | Herpes virus infections (HSV1 and HSV2) of skin can occur anywhere from mucosal surfaces to normal skin. These include herpes labialis, herpes genitalis, herpetic whitlow H (finger). |
| **Molluscum contagiosum** | Umbilicated papules I caused by a poxvirus. While frequently seen in children, it may be sexually transmitted in adults. |
| **Varicella zoster virus** | Causes varicella (chickenpox) and zoster (shingles). Varicella presents with multiple crops of lesions in various stages from vesicles to crusts. Zoster is a reactivation of the virus in dermatomal distribution (unless it is disseminated). |
| **Hairy leukoplakia** | Irregular, white, painless plaques on lateral tongue that cannot be scraped off J. EBV mediated. Occurs in patients living with HIV, organ transplant recipients. Contrast with thrush (scrapable) and leukoplakia (precancerous). |

## Autoimmune blistering skin disorders

| | Pemphigus vulgaris | Bullous pemphigoid |
|---|---|---|
| PATHOPHYSIOLOGY | Potentially fatal. Most commonly seen in older adults. Type II hypersensitivity reaction.<br>IgG antibodies against desmoglein-1 and/or desmoglein-3 (component of desmosomes, which connect keratinocytes in the stratum spinosum). | Less severe than pemphigus vulgaris. Most commonly seen in older adults. Type II hypersensitivity reaction.<br>IgG antibodies against hemidesmosomes (epidermal basement membrane; antibodies are "bullow" the epidermis). |
| GROSS MORPHOLOGY | Flaccid intraepidermal bullae A caused by acantholysis (separation of keratinocytes, "row of tombstones" on H&E stain); oral mucosa is involved. Nikolsky sign ⊕. | Tense blisters C containing eosinophils; oral mucosa spared. Nikolsky sign ⊖. |
| IMMUNOFLUORESCENCE | Reticular pattern around epidermal cells B. | Linear pattern at epidermal-dermal junction D. |



## Other blistering skin disorders

| | |
|---|---|
| **Dermatitis herpetiformis** | Pruritic papules, vesicles, and bullae (often found on elbows, knees, buttocks) A. Deposits of IgA at tips of dermal papillae. Associated with celiac disease. Treatment: dapsone, gluten-free diet. |
| **Erythema multiforme** | Associated with infections (eg, *Mycoplasma pneumoniae*, HSV), drugs (eg, sulfa drugs, β-lactams, phenytoin). Presents with multiple types of lesions—macules, papules, vesicles, target lesions (look like targets with multiple rings and dusky center showing epithelial disruption) B. |
| **Stevens-Johnson syndrome** | Characterized by fever, bullae formation and necrosis, sloughing of skin at dermal-epidermal junction (⊕ Nikolsky), high mortality rate. Typically mucous membranes are involved C D. Targetoid skin lesions may appear, as seen in erythema multiforme. Usually associated with adverse drug reaction. Toxic epidermal necrolysis (TEN) E F is more severe form of SJS involving > 30% body surface area. 10–30% involvement denotes SJS-TEN. |


## Lower extremity ulcers

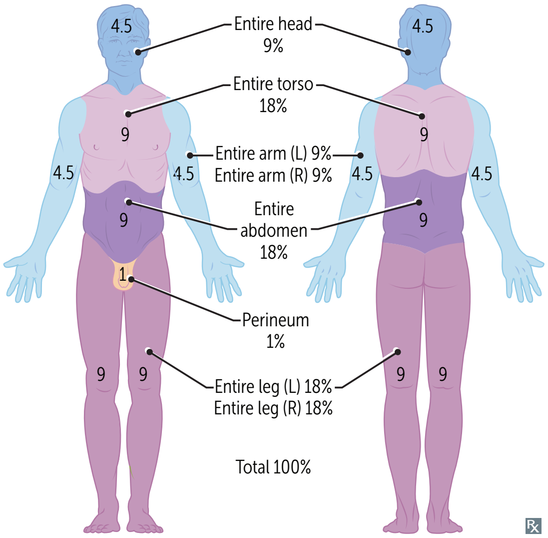
| | Venous ulcer | Arterial ulcer | Neuropathic ulcer |
|---|---|---|---|
| ETIOLOGY | Chronic venous insufficiency; most common ulcer type | Peripheral artery disease (eg, atherosclerotic stenosis) | Peripheral neuropathy (eg, diabetic foot) |
| LOCATION | Gaiter area (ankle to midcalf), typically over malleoli | Distal toes, anterior shin, pressure points | Bony prominences (eg, metatarsal heads, heel) |
| APPEARANCE | Irregular border, shallow, exudative A | Symmetric with well-defined punched out appearance B | Hyperkeratotic edge with undermined borders C |
| PAIN | Mild to moderate | Severe | Absent |
| ASSOCIATED SIGNS | Telangiectasias, varicose veins, edema, stasis dermatitis (erythematous eczematous patches) | Signs of arterial insufficiency including cold, pale, atrophic skin with hair loss and nail dystrophy, absent pulses | Claw toes, Charcot joints, absent reflexes |

## Miscellaneous skin disorders

| | |
|---|---|
| **Acanthosis nigricans** | Epidermal hyperplasia causing symmetric, hyperpigmented thickening of skin, especially in axilla or on neck A B. Associated with insulin resistance (eg, diabetes, obesity, Cushing syndrome, PCOS), visceral malignancy (eg, gastric adenocarcinoma). |
| **Actinic keratosis** | Premalignant lesions caused by sun exposure. Small, rough, erythematous or brownish papules or plaques C D. Risk of squamous cell carcinoma is proportional to degree of epithelial dysplasia. |
| **Erythema nodosum** | Painful, raised inflammatory lesions of subcutaneous fat (panniculitis), usually on anterior shins. Often idiopathic, but can be associated with sarcoidosis, coccidioidomycosis, histoplasmosis, TB, streptococcal infections E, leprosy F, inflammatory bowel disease. |
| **Lichen Planus** | **P**ruritic, **p**urple, **p**olygonal **p**lanar **p**apules and **p**laques are the **6 P's** of lichen **P**lanus G H. Mucosal involvement manifests as Wickham striae (reticular white lines) and hypergranulosis. Sawtooth infiltrate of lymphocytes at dermal-epidermal junction. Associated with hepatitis C. |
| **Pityriasis rosea** | "Herald patch" I followed days later by other scaly erythematous plaques, often in a "Christmas tree" distribution on trunk J. Multiple pink plaques with collarette scale. Self-resolving in 6–8 weeks. |
| **Sunburn** | Acute cutaneous inflammatory reaction due to excessive UV irradiation. Causes DNA mutations, inducing apoptosis of keratinocytes. UV**B** is dominant in sun**B**urn, UV**A** in t**A**nning and photo**A**ging. Exposure to UVA and UVB ↑ risk of skin cancer. |

**Rule of 9's**

The extent of a burn injury can be estimated as a percentage of the body surface area.




**Burn classification**

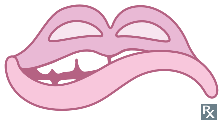
| DEPTH | INVOLVEMENT | APPEARANCE | SENSATION |
|---|---|---|---|
| **Superficial burn** | Epidermis only | Similar to sunburn; localized, dry, blanching redness with no blisters | Painful |
| **Superficial partial-thickness burn** | Epidermis and papillary dermis | Blisters, blanches with pressure, swollen, warm | Painful to temperature and air |
| **Deep partial-thickness burn** | Epidermis and reticular dermis | Blisters (easily unroofed), does not blanch with pressure | Painless; perception of pressure only |
| **Full-thickness burn** | Epidermis and full-thickness dermis | White, waxy, dry, inelastic, leathery, does not blanch with pressure | Painless; perception of deep pressure only |
| **Deeper injury burn** | Epidermis, dermis, and involvement of underlying tissue (eg, fascia, muscle) | White, dry, inelastic, does not blanch with pressure | Painless; some perception of deep pressure |

**Skin cancer**

Basal cell carcinoma more common above upper lip

Squamous cell carcinoma more common below lower lip

Sun exposure strongly predisposes to skin cancer.



**Basal cell carcinoma**

Most common skin cancer. Found in sun-exposed areas of body (eg, face). Locally invasive, but rarely metastasizes. Waxy, pink, pearly nodules, commonly with telangiectasias, rolled borders A, central crusting or ulceration. BCCs also appear as nonhealing ulcers with infiltrating growth B or as a scaling plaque (superficial BCC) C. Basal cell tumors have "palisading" (aligned) nuclei D.

**Keratoacanthoma**

Seen in middle-aged and elderly individuals. Rapidly growing, resembles squamous cell carcinoma. Presents as dome-shaped nodule with keratin-filled center. Grows rapidly (4-6 weeks) and may spontaneously regress E.

**Melanoma**

Common tumor with significant risk of metastasis. S-100 tumor marker. Associated with dysplastic nevi; people with lighter skin tones are at ↑ risk. Depth of tumor (Breslow thickness) correlates with risk of metastasis. Look for the ABCDEs: Asymmetry, Border irregularity, Color variation, Diameter > 6 mm, and Evolution over time. At least 4 different types of melanoma, including superficial spreading F, nodular G, lentigo maligna H, and acral lentiginous (highest prevalence in people with darker skin tones) I. Often driven by activating mutation in BRAF kinase. Primary treatment is excision with appropriately wide margins. Advanced melanoma also treated with immunotherapy (eg, ipilimumab) and/or BRAF inhibitors (eg, vemurafenib).

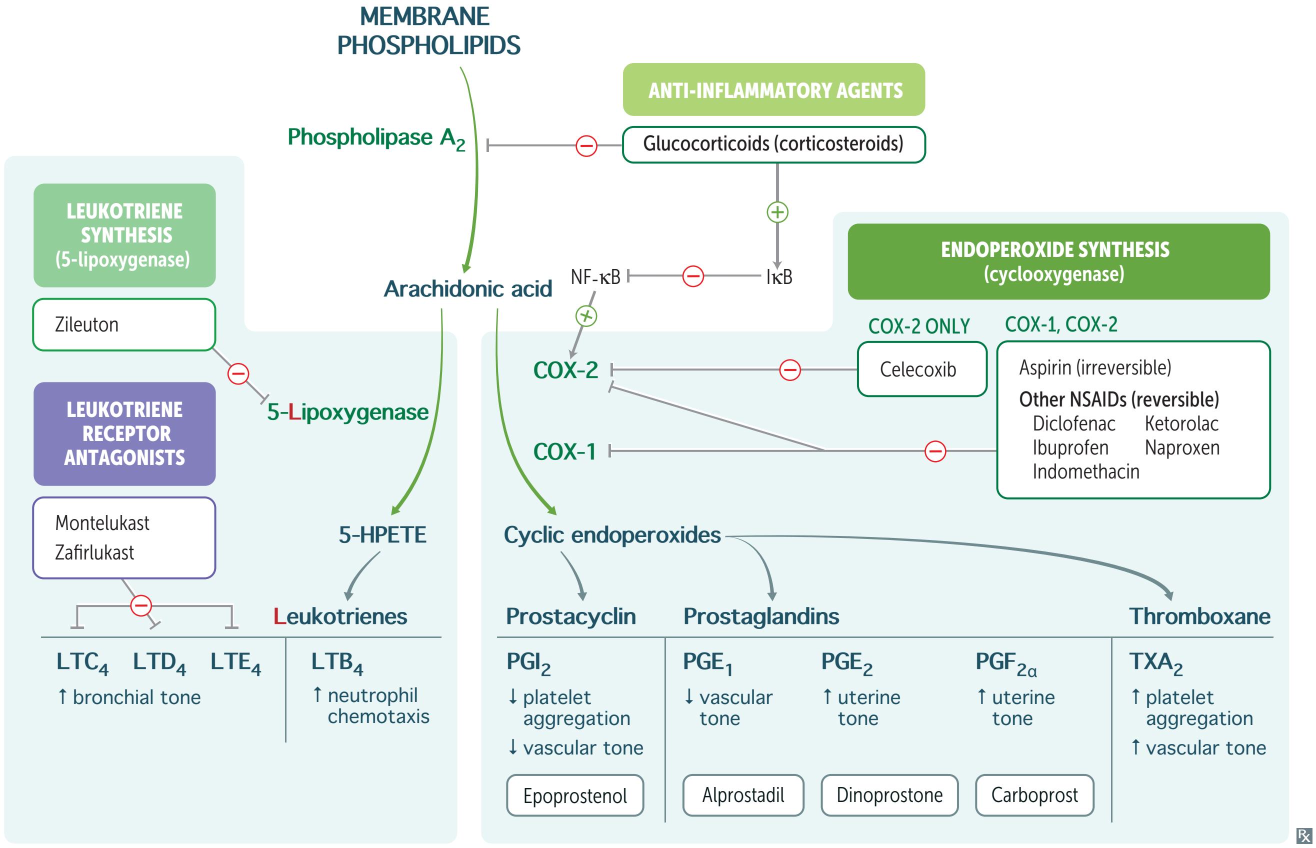
**Squamous cell carcinoma**

Second most common skin cancer. Associated with immunosuppression, chronic nonhealing wounds, and occasionally arsenic exposure. Commonly appears on face J, lower lip K, ears, hands. Locally invasive, may spread to lymph nodes, and will rarely metastasize. Ulcerative red lesions. Histopathology: keratin "pearls" L.

Actinic keratosis, a scaly plaque, is a precursor to squamous cell carcinoma.

▸ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PHARMACOLOGY

## Arachidonic acid pathways




| | |
|---|---|
| $LTB_4$ is a **neutrophil** chemotactic agent. | **Neutrophils** arrive "**B4**" others. |
| **$PGI_2$** inhibits platelet aggregation and promotes vasodilation. | **P**latelet-**G**athering **I**nhibitor. |

## Acetaminophen

| | |
|---|---|
| MECHANISM | Reversibly inhibits cyclooxygenase, mostly in CNS. Inactivated peripherally. |
| CLINICAL USE | Antipyretic, analgesic, but not anti-inflammatory. Used instead of aspirin to avoid Reye syndrome in children with viral infection. |
| ADVERSE EFFECTS | Overdose produces hepatic necrosis; acetaminophen metabolite (NAPQI) depletes glutathione and forms toxic tissue byproducts in liver. N-acetylcysteine is antidote—regenerates glutathione. |

## Aspirin

| | |
|---|---|
| MECHANISM | NSAID that irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) by covalent acetylation → ↓ synthesis of $TXA_2$ and prostaglandins. ↑ bleeding time. No effect on PT, PTT. Effect lasts until new platelets are produced. |
| CLINICAL USE | Low dose (< 300 mg/day): ↓ platelet aggregation. Intermediate dose (300–2400 mg/day): antipyretic and analgesic. High dose (2400–4000 mg/day): anti-inflammatory. |
| ADVERSE EFFECTS | Gastric ulceration, tinnitus (CN VIII), allergic reactions (especially in patients with asthma or nasal polyps). Chronic use can lead to acute kidney injury, interstitial nephritis, GI bleeding. Risk of Reye syndrome in children treated with aspirin for viral infection. Toxic doses cause respiratory alkalosis early, but transitions to mixed metabolic acidosis-respiratory alkalosis. Treatment of overdose: $NaHCO_3$. |

## Celecoxib

| | |
|---|---|
| MECHANISM | Reversibly and **sele**ctively inh**ib**its the cyclooxygenase (**COX**) isoform 2 ("**Selecoxib**"), which is found in inflammatory cells and vascular endothelium and mediates inflammation and pain; spares COX-1, which helps maintain gastric mucosa. Thus, does not have the corrosive effects of other NSAIDs on the GI lining. Spares platelet function as $TXA_2$ production is dependent on COX-1. |
| CLINICAL USE | Rheumatoid arthritis, osteoarthritis. |
| ADVERSE EFFECTS | ↑ risk of thrombosis, sulfa allergy. |

## Nonsteroidal anti-inflammatory drugs

Ibuprofen, naproxen, indomethacin, ketorolac, diclofenac, meloxicam, piroxicam.

| | |
|---|---|
| MECHANISM | Reversibly inhibit cyclooxygenase (both COX-1 and COX-2). Block prostaglandin synthesis. |
| CLINICAL USE | Antipyretic, analgesic, anti-inflammatory. Indomethacin is used to close a PDA. |
| ADVERSE EFFECTS | Interstitial nephritis, gastric ulcer (prostaglandins protect gastric mucosa), renal ischemia (prostaglandins vasodilate afferent arteriole), aplastic anemia. |

## Leflunomide

| | |
|---|---|
| MECHANISM | Reversibly inhibits dihydroorotate dehydrogenase, preventing pyrimidine synthesis. Suppresses T-cell proliferation. |
| CLINICAL USE | Rheumatoid arthritis, psoriatic arthritis. |
| ADVERSE EFFECTS | Diarrhea, hypertension, hepatotoxicity, teratogenicity. |

## Bisphosphonates

Alendronate, ibandronate, risedronate, zoledronate.

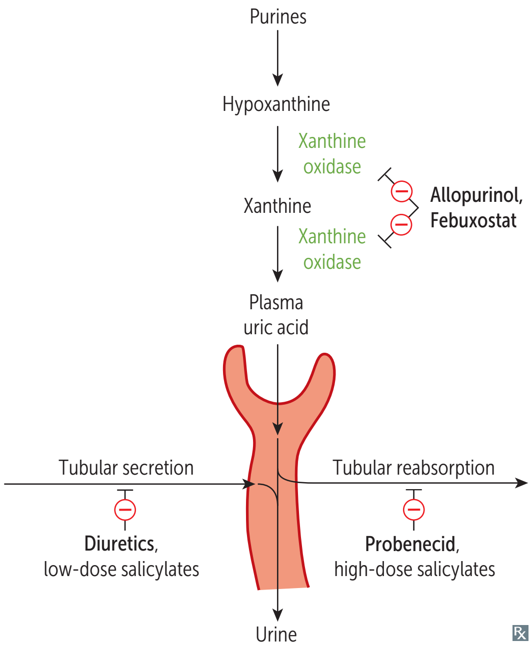
| | |
|---|---|
| MECHANISM | Pyrophosphate analogs; bind hydroxyapatite in bone, inhibiting osteoclast activity. |
| CLINICAL USE | Osteoporosis, hypercalcemia, Paget disease of bone, metastatic bone disease, osteogenesis imperfecta. |
| ADVERSE EFFECTS | Esophagitis (if taken orally, patients are advised to take with water and remain upright for 30 minutes), osteonecrosis of jaw, atypical femoral stress fractures. |

## Teriparatide

| | |
|---|---|
| MECHANISM | Recombinant PTH analog. ↑ osteoblastic activity when administered in pulsatile fashion. |
| CLINICAL USE | Osteoporosis. Causes ↑ bone growth compared to antiresorptive therapies (eg, bisphosphonates). |
| ADVERSE EFFECTS | ↑ risk of osteosarcoma (avoid use in patients with Paget disease of the bone or unexplained elevation of alkaline phosphatase). Avoid in patients who have had prior cancers or radiation therapy. Transient hypercalcemia. |

## Gout drugs

| Chronic gout drugs (preventive) | | |
|---|---|---|
| **Allopurinol** | Competitive inhibitor of xanthine oxidase → ↓ conversion of hypoxanthine and xanthine to urate. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy. ↑ concentrations of xanthine oxidase active metabolites, azathioprine, and 6-MP. | **All** **p**ainful **fl**ares are **pr**eventable. |
| **Pegloticase** | Recombinant uricase catalyzing uric acid to allantoin (a more water-soluble product). | |
| **Febuxostat** | Inhibits xanthine oxidase. Think, "febu-**xo**-**stat** makes **X**anthine **O**xidase **stat**ic." | |
| **Probenecid** | Inhibits reabsorption of uric acid in proximal convoluted tubule (also inhibits secretion of penicillin). Can precipitate uric acid calculi. | |
| **Acute gout drugs** | | |
| **NSAIDs** | Any NSAID. Use salicylates with caution (may decrease uric acid excretion, particularly at low doses). | |
| **Glucocorticoids** | Oral, intra-articular, or parenteral. | |
| **Colchicine** | Binds and stabilizes tubulin to inhibit microtubule polymerization, impairing neutrophil chemotaxis and degranulation. Acute and prophylactic value. GI, neuromyopathic side effects. Can also cause myelosupression, nephrotoxicity. | |



### TNF-α inhibitors

| DRUG | MECHANISM | CLINICAL USE | ADVERSE EFFECTS |
|---|---|---|---|
| **Etanercept** | Fusion protein (decoy receptor for TNF-α + $IgG_1$ Fc), produced by recombinant DNA. Etanercept intercepts TNF. | Rheumatoid arthritis, psoriasis, ankylosing spondylitis | Predisposition to infection, including reactivation of latent TB, since TNF is important in granuloma formation and stabilization. Can also lead to drug-induced lupus. |
| **Infliximab, adalimumab, certolizumab, golimumab** | Anti-TNF-α monoclonal antibody. | Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis | |

HIGH-YIELD SYSTEMS

# Neurology and Special Senses

*"We are all now connected by the Internet, like neurons in a giant brain."*

—Stephen Hawking

*"Anything's possible if you've got enough nerve."*

—J.K. Rowling, *Harry Potter and the Order of the Phoenix*

*"I like nonsense; it wakes up the brain cells."*

—Dr. Seuss

*"I believe in an open mind, but not so open that your brains fall out."*

—Arthur Hays Sulzberger

*"The chief function of the body is to carry the brain around."*

—Thomas Edison

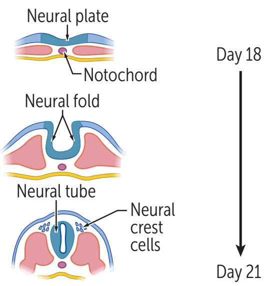
*"Exactly how [the brain] operates remains one of the biggest unsolved mysteries, and it seems the more we probe its secrets, the more surprises we find."*

—Neil deGrasse Tyson

Understand the difference between the findings and underlying anatomy of upper motor neuron and lower motor neuron lesions. Know the major motor, sensory, cerebellar and visual pathways and their respective locations in the CNS. Connect key neurological associations with certain pathologies (eg, cerebellar lesions, stroke manifestations, Brown-Séquard syndrome). Recognize common findings on MRI/CT (eg, ischemic and hemorrhagic stroke) and on neuropathology (eg, neurofibrillary tangles and Lewy bodies). High-yield medications include those used to treat epilepsy, Parkinson disease, migraine, and pain (eg, opioids).

## ▸ NEUROLOGY—EMBRYOLOGY

### Neural development

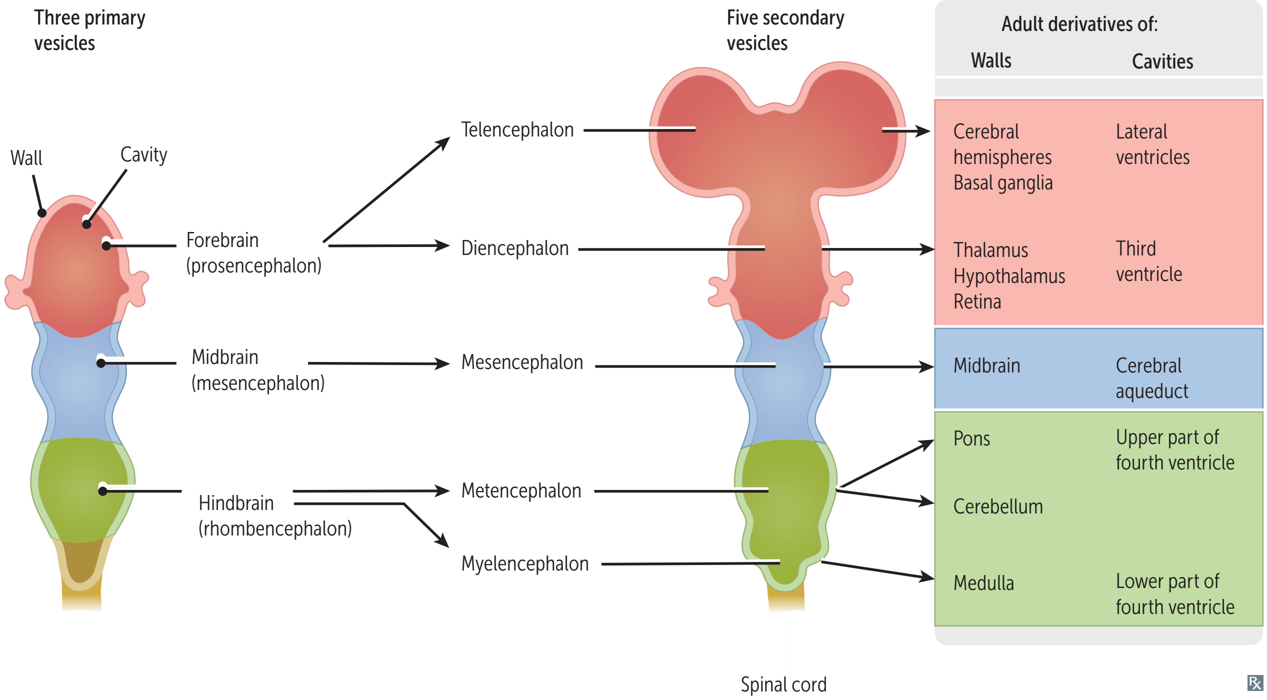



Notochord induces overlying ectoderm to differentiate into neuroectoderm and form neural plate.
Neural plate gives rise to neural tube and neural crest cells.
Notochord becomes nucleus pulposus of intervertebral disc in adults.

Alar plate (dorsal): sensory; regulated by TGF-β (including bone morphogenetic protein [*BMP*])
Basal plate (ventral): motor; regulated by sonic hedgehog gene (*SHH*)
Same orientation as spinal cord

### Regional specification of developing brain

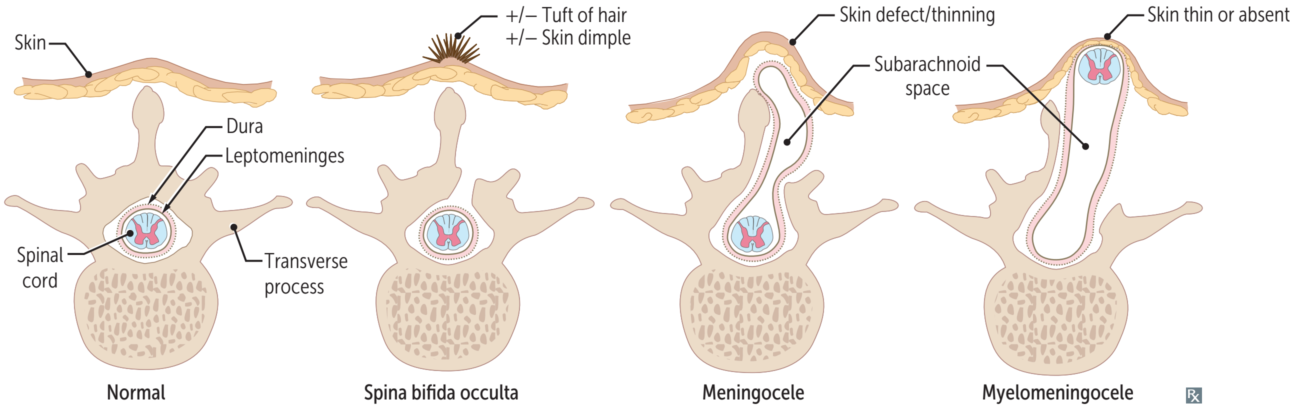
Telencephalon is the 1st part. **Di**encephalon is the **2nd** part. The rest are arranged alphabetically: **mes**encephalon, **met**encephalon, **my**elencephalon.



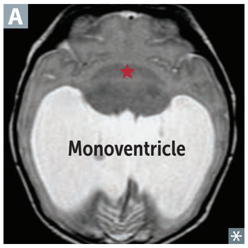

### Central and peripheral nervous systems origins

Neuroepithelia in neural tube—CNS neurons, CNS glial cells (astrocytes, oligodendrocytes, ependymal cells).
Neural crest—PNS neurons (dorsal root ganglia, autonomic ganglia [sympathetic, parasympathetic, enteric]), PNS glial cells (Schwann cells, satellite cells), adrenal medulla, melanocytes, face/branchial arch mesenchyme.
**M**esoderm—**m**icroglia (like **m**acrophages).

| | |
|---|---|
| **Neural tube defects** | Neuropores fail to fuse by the 4th week of development → persistent connection between amniotic cavity and spinal canal. Associated with diabetes and folate deficiency during pregnancy. ↑ α-fetoprotein (AFP) in amniotic fluid and serum (except spina bifida occulta = normal AFP). ↑ acetylcholinesterase (AChE) in amniotic fluid is a helpful confirmatory test. |
| **Spina bifida occulta** | Failure of caudal neuropore to close, but no herniation. Usually seen at lower vertebral levels. Dura is intact. Associated with tuft of hair or skin dimple at level of bony defect. |
| **Meningocele** | Meninges (but no neural tissue) herniate through bony defect. |
| **Myelomeningocele** | Meninges and neural tissue (eg, cauda equina) herniate through bony defect. |
| **Myeloschisis** | Also called rachischisis. Exposed, unfused neural tissue without skin/meningeal covering. |
| **Anencephaly** | Failure of rostral neuropore to close → no forebrain, open calvarium. Clinical findings: polyhydramnios (no swallowing center in brain). |



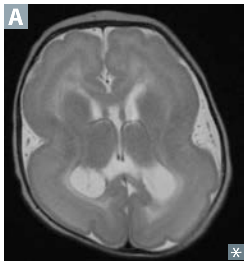

## Holoprosencephaly




Developmental field defect characterized by failure of embryonic forebrain (prosencephalon) to separate into 2 cerebral hemispheres; usually occurs during weeks 3–4 of development. May be related to mutations in sonic hedgehog signaling pathway. Associated with other midline defects including cleft lip/palate (moderate form) and cyclopia (severe form). ↑ risk for pituitary dysfunction (eg, diabetes insipidus). May be seen with Patau syndrome (trisomy 13) and maternal alcohol use.

MRI reveals monoventricle **A** and fusion of basal ganglia (star in **A**).

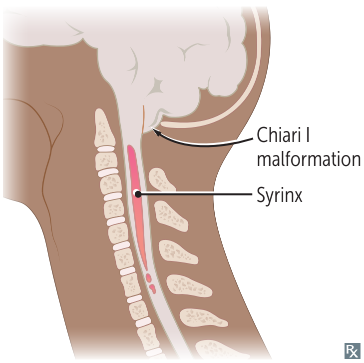
## Lissencephaly

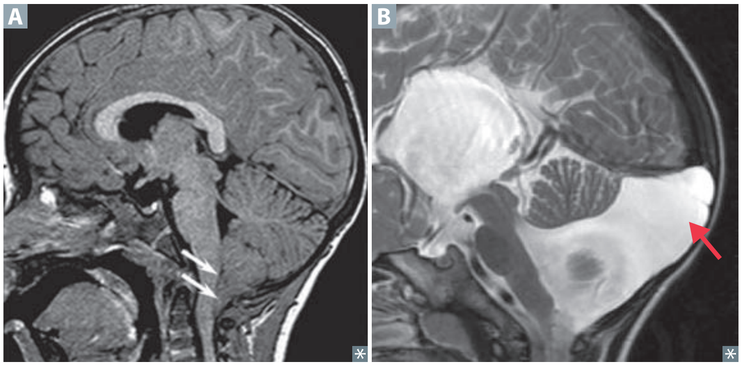



Failure of neuronal migration resulting in a "smooth brain" that lacks sulci and gyri **A**. May be associated with microcephaly, ventriculomegaly, hydrocephalus.

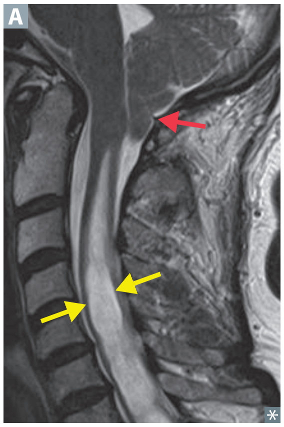
## Posterior fossa malformations

| | |
|---|---|
| **Chiari I malformation** | Ectopia of cerebellar **tonsils** inferior to foramen magnum (1 structure) A. Congenital, usually asymptomatic in childhood, manifests in adulthood with headaches and cerebellar symptoms. Associated with spinal cavitations (eg, syringomyelia). |
| **Chiari II malformation** | Herniation of **cerebellum** (vermis and tonsils) and **medulla** (2 structures) through foramen magnum → noncommunicating hydrocephalus. Usually associated with aqueductal stenosis, lumbosacral myelomeningocele (may present as paralysis/sensory loss at and below the level of the lesion). More severe than Chiari I, usually presents early in life. |
| **Dandy-Walker malformation** | Agenesis of cerebellar vermis → cystic enlargement of 4th ventricle (arrow in B) that fills the enlarged posterior fossa. Associated with noncommunicating hydrocephalus, spina bifida. |



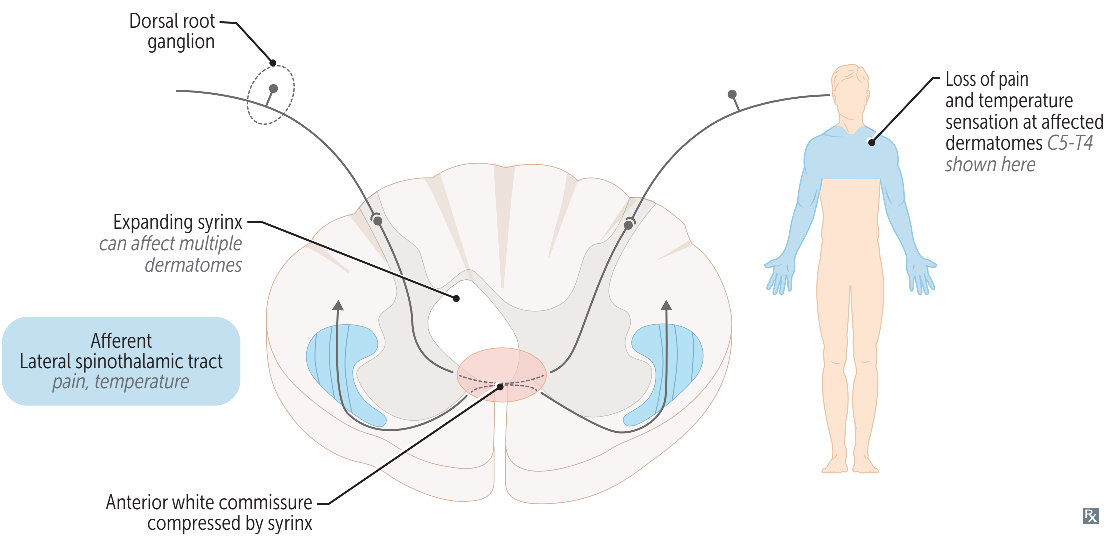




## Syringomyelia

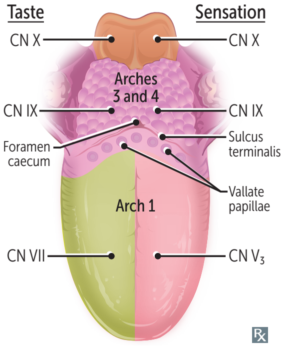



Cystic cavity (syrinx) within central canal of spinal cord (yellow arrows in A). Fibers crossing in anterior white commissure (spinothalamic tract) are typically damaged first. Results in a "cape-like," bilateral, symmetrical loss of pain and temperature sensation in upper extremities (fine touch sensation is preserved).

Associated with Chiari I malformation (red arrow in A shows low-lying cerebellar tonsils), scoliosis and other congenital malformations; acquired causes include trauma and tumors. Most common location cervical > thoracic >> lumbar. **Syrin**x = tube, as in "**syrin**ge."



### Tongue development




1st pharyngeal arch forms anterior 2/3 of tongue (sensation via CN $V_3$, taste via CN VII).
3rd and 4th pharyngeal arches form posterior 1/3 of tongue (sensation and taste mainly via CN IX, extreme posterior via CN X).
Motor innervation is via CN XII to hyoglossus (retracts and depresses tongue), **geni**oglossus (**protrudes** tongue), and **styl**oglossus (draws sides of tongue upward to create a trough for swallowing).
Motor innervation is via CN X to palatoglossus (elevates posterior tongue during swallowing).

Taste—CN VII, IX, X (solitary nucleus).
Pain—CN $V_3$, IX, X.
Motor—CN X, XII.

The **genie** comes **out** of the lamp in **style**.

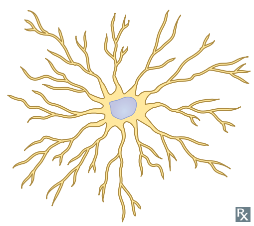
CN **10** innervates pala**ten**glossus.

## ▶ NEUROLOGY—ANATOMY AND PHYSIOLOGY

### Neurons

Signal-transmitting cells of the nervous system. Permanent cells—do not divide in adulthood.
Signal-relaying cells with dendrites (receive input), cell bodies, and axons (send output). Cell bodies and dendrites can be seen on Nissl staining (stains RER). RER is not present in the axon. Neuron markers: neurofilament protein, synaptophysin.

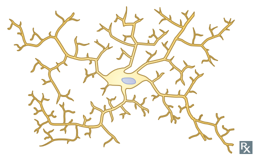
### Astrocytes



Most common glial cell type in CNS.
Physical support, repair, removal of excess neurotransmitter, component of blood-brain barrier, glycogen fuel reserve buffer. Reactive gliosis in response to neural injury.

Derived from neuroectoderm.
Astrocyte marker: GFAP.

### Microglia



Phagocytic scavenger cells of CNS. Activation in response to tissue damage → release of inflammatory mediators (eg, nitric oxide, glutamate). Not readily discernible by Nissl stain.

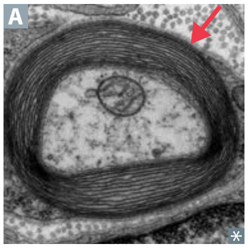
Derived from mesoderm.
HIV-infected microglia fuse to form multinucleated giant cells in CNS seen in HIV-associated dementia.

### Ependymal cells

Ciliated simple columnar glial cells lining ventricles and central canal of spinal cord. Apical surfaces are covered with cilia (which circulate CSF) and microvilli (which help with CSF absorption).

Derived from neuroectoderm.
Specialized ependymal cells (choroid plexus) produce CSF.

## Myelin




↑ conduction velocity of signals transmitted down axons → saltatory conduction of action potential at the nodes of Ranvier, where there are high concentrations of $Na^+$ channels.

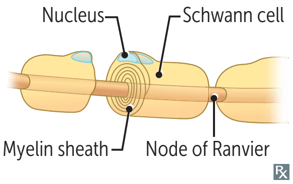
In CNS (including CN II), myelin is synthesized by oligodendrocytes; in PNS (including CN III-XII), myelin is synthesized by Schwann cells.

Myelin (arrow in A) wraps and insulates axons: ↓ membrane capacitance, ↑ membrane resistance, ↑ space (length) constant, ↓ time constant.

CNS: Oligodendrocytes.

PNS: Schwann cells. COPS

## Schwann cells



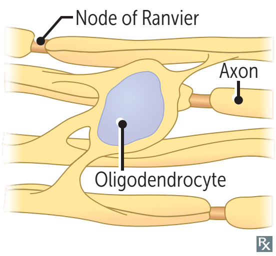

Promote axonal regeneration. Derived from neural crest.

Each "Schwone" cell myelinates only 1 PNS axon.

Injured in Guillain-Barré syndrome.

Schwann cell marker: S100.

## Oligodendrocytes



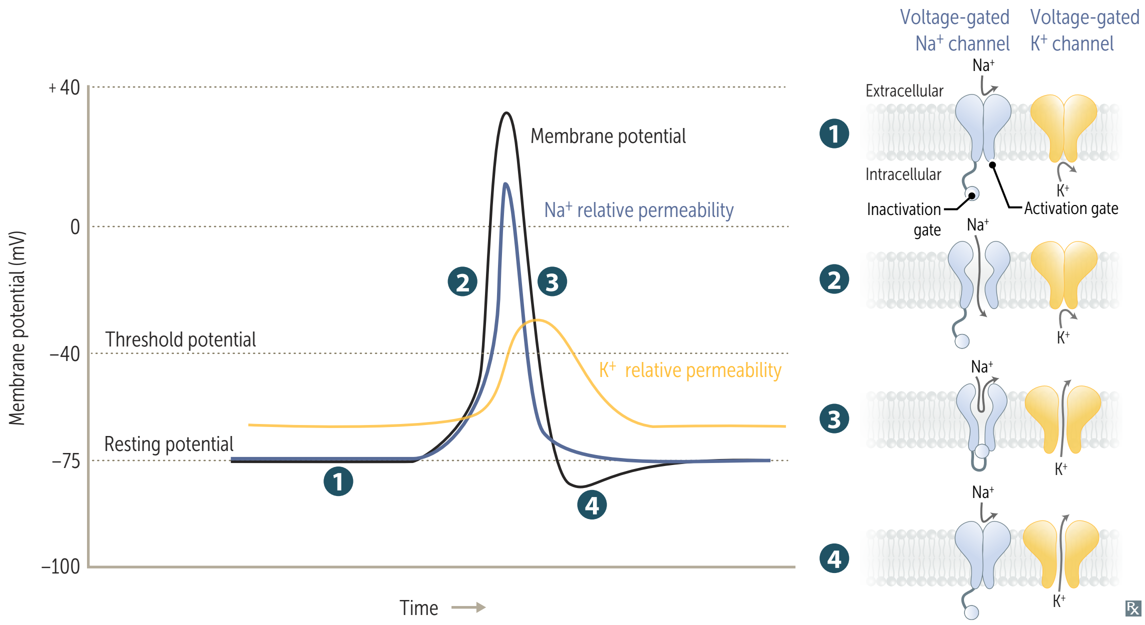

Myelinate axons of neurons in CNS. Each oligodendrocyte can myelinate many axons (~ 30). Predominant type of glial cell in white matter.

Derived from neuroectoderm.

"Fried egg" appearance histologically.

Injured in multiple sclerosis, progressive multifocal leukoencephalopathy (PML), leukodystrophies.

## Neuron action potential

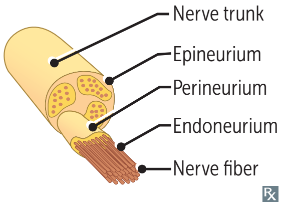



❶ Resting membrane potential: membrane is more permeable to $K^+$ than $Na^+$ at rest. Voltage-gated $Na^+$ and $K^+$ channels are closed.
❷ Membrane depolarization: $Na^+$ activation gate opens → $Na^+$ flows inward.
❸ Membrane repolarization: $Na^+$ inactivation gate closes at peak potential, thus stopping $Na^+$ inflow. $K^+$ activation gate gate opens → $K^+$ flows outward.
❹ Membrane hyperpolarization: $K^+$ activation gates are slow to close → excess $K^+$ efflux and brief period of hyperpolarization. Voltage-gated $Na^+$ channels switch back to resting state. $Na^+/K^+$ pump restores ions concentration.

## Sensory receptors

| RECEPTOR TYPE | SENSORY NEURON FIBER TYPE | LOCATION | SENSES |
|---|---|---|---|
| **Free nerve endings** | Aδ—**fast**, myelinated fibers<br>C—**slow**, unmyelinated<br>**A Delta** plane is **fast**, but a tax**C** is **slow** | All tissues except cartilage and eye lens; numerous in skin | Pain, temperature |
| **Meissner corpuscles** | Large, myelinated fibers; adapt quickly | Glabrous (hairless) skin | Dynamic, fine/light touch, position sense, low-frequency vibration, skin indentation |
| **Pacinian corpuscles** | Large, myelinated fibers; adapt quickly | Deep skin layers, ligaments, joints | High-frequency vibration, pressure |
| **Merkel discs** | Large, myelinated fibers; adapt slowly | Finger tips, superficial skin | Pressure, deep static touch (eg, shapes, edges) |
| **Ruffini corpuscles** | Large, myelinated fiber intertwined among collagen fiber bundles; adapt slowly | Finger tips, joints | Stretch, joint angle change |

## Peripheral nerve



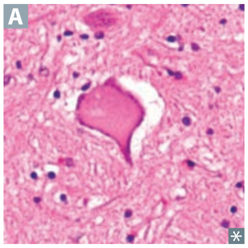

Endoneurium—thin, supportive connective tissue that ensheathes and supports individual myelinated nerve fibers. May be affected in Guillain-Barré syndrome.

Perineurium (blood-nerve permeability barrier)—surrounds a fascicle of nerve fibers.

Epineurium—dense connective tissue that surrounds entire nerve (fascicles and blood vessels).

*Endo* = inner
*Peri* = around
*Epi* = outer

## Chromatolysis

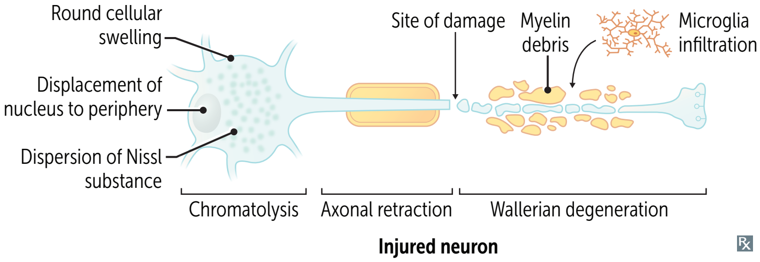



Reaction of neuronal cell body to axonal injury. Changes reflect ↑ protein synthesis in effort to repair the damaged axon. Characterized by:

- Round cellular swelling A
- Displacement of the nucleus to the periphery
- Dispersion of Nissl substance throughout cytoplasm

Wallerian degeneration—disintegration of the axon and myelin sheath distal to site of axonal injury with macrophages removing debris.

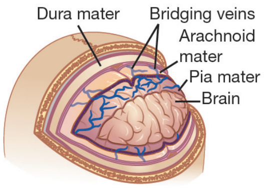
Proximal to the injury, the axon retracts, and the cell body sprouts new protrusions that grow toward other neurons for potential reinnervation. Serves as a preparation for axonal regeneration and functional recovery.




## Neurotransmitter changes with disease

| | LOCATION OF SYNTHESIS | ANXIETY | DEPRESSION | SCHIZOPHRENIA | ALZHEIMER DISEASE | HUNTINGTON DISEASE | PARKINSON DISEASE |
|---|---|---|---|---|---|---|---|
| **Acetylcholine** | Basal nucleus of Meynert (forebrain) | | | | ↓ | ↓ | ↑ |
| **Dopamine** | Ventral tegmentum, SNc (midbrain) | | ↓ | ↑ | | ↑ | ↓ |
| **GABA** | Nucleus accumbens (basal ganglia) | ↓ | | | | ↓ | |
| **Norepinephrine** | Locus ceruleus (pons) | ↑ | ↓ | | | | |
| **Serotonin** | Raphe nuclei (brain stem) | ↓ | ↓ | | | | ↓ |

## Meninges

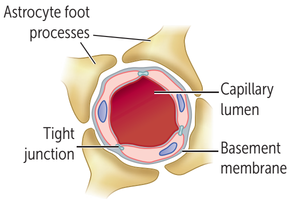



Three membranes that surround and protect the brain and spinal cord:
- Dura mater—thick outer layer closest to skull. Derived from mesoderm.
- Arachnoid mater—middle layer, contains web-like connections. Derived from neural crest.
- Pia mater—thin, fibrous inner layer that firmly adheres to brain and spinal cord. Derived from neural crest.

CSF flows in the subarachnoid space, located between arachnoid and pia mater.

Epidural space—potential space between dura mater and skull/vertebral column containing fat and blood vessels. Site of blood collection associated with middle meningeal artery injury.

## Blood-brain barrier




Prevents circulating blood substances (eg, bacteria, drugs) from reaching the CSF/CNS. Formed by 4 structures:
- Tight junctions between nonfenestrated capillary endothelial cells
- Basement membrane
- Astrocyte foot processes
- Pericytes

Glucose and amino acids cross slowly by carrier-mediated transport mechanisms.

Nonpolar/lipid-soluble substances cross rapidly via diffusion.

Circumventricular organs with fenestrated capillaries and no blood-brain barrier allow molecules in blood to affect brain function (eg, area postrema—vomiting after chemotherapy; OVLT [organum vasculosum lamina terminalis]—osmoreceptors) or neurosecretory products to enter circulation (eg, neurohypophysis—ADH release).

Infarction and/or neoplasm destroys endothelial cell tight junctions → vasogenic edema.

Hyperosmolar agents (eg, mannitol) can disrupt the BBB → ↑ permeability of medications.

## Vomiting center

Coordinated by nucleus tractus solitarius (NTS) in the medulla, which receives information from the chemoreceptor trigger zone (CTZ, located within area postrema (pronounce "puke"-strema) in 4th ventricle), GI tract (via vagus nerve), vestibular system, and CNS.

CTZ and adjacent vomiting center nuclei receive input from 5 major receptors: muscarinic ($M_1$), dopamine ($D_2$), histamine ($H_1$), serotonin (5-$HT_3$), and neurokinin (NK-1) receptors.
- 5-$HT_3$, $D_2$, and NK-1 antagonists used to treat chemotherapy-induced vomiting.
- $H_1$ and $M_1$ antagonists treat motion sickness; $H_1$ antagonists treat hyperemesis gravidarum.

**Sleep physiology**

Sleep cycle is regulated by the circadian rhythm, which is driven by suprachiasmatic nucleus (SCN) of the hypothalamus. Circadian rhythm controls nocturnal release of ACTH, prolactin, melatonin, norepinephrine: SCN → norepinephrine release → pineal gland → ↑ melatonin. SCN is regulated by environment (eg, light).

Two stages: rapid-eye movement (REM) and non-REM.

Alcohol, benzodiazepines, and barbiturates are associated with ↓ REM sleep and N3 sleep; norepinephrine also ↓ REM sleep.

Benzodiazepines are useful for night terrors and sleepwalking by ↓ N3 and REM sleep.

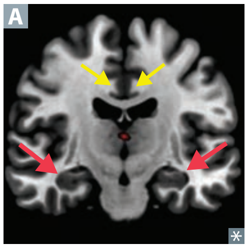
| SLEEP STAGE (% OF TOTAL SLEEP TIME IN YOUNG ADULTS) | DESCRIPTION | EEG WAVEFORM AND NOTES |
|---|---|---|
| **Awake (eyes open)** | Alert, active mental concentration. | **B**eta (highest frequency, lowest amplitude). |
| **Awake (eyes closed)** | | **A**lpha. |
| **Non-REM sleep** | | |
| Stage N1 (5%) | Light sleep. | **T**heta. |
| Stage N2 (45%) | Deeper sleep; when bruxism ("**two**th" [tooth] grinding) occurs. | **S**leep spindles and K complexes. |
| Stage N3 (25%) | Deepest non-REM sleep (slow-wave sleep); **sleepwalking**, night terrors, and **bedwetting** occur (**wee** and **flee** in N3). | **D**elta (lowest frequency, highest amplitude), deepest sleep stage. |
| **REM sleep (25%)** | Loss of motor tone, ↑ brain $O_2$ use, variable pulse/BP, ↑ ACh. REM is when dreaming, nightmares, and penile/clitoral tumescence occur; may serve memory processing function.<br>Extraocular movements due to activity of PPRF (paramedian pontine reticular formation/conjugate gaze center).<br>Occurs every 90 minutes, and duration ↑ through the night. | **B**eta.<br>Changes in elderly: ↓ REM, ↓ N3, ↑ sleep latency, ↑ early awakenings.<br>Changes in depression: ↑ REM sleep time, ↓ REM latency, ↓ N3, repeated nighttime awakenings, early morning awakening (terminal insomnia).<br>Change in narcolepsy: ↓ REM latency.<br>At night, **BATS D**rink **B**lood. |

| | | |
|---|---|---|
| **Hypothalamus** | Maintains homeostasis by regulating Thirst and water balance, controlling Adenohypophysis (anterior pituitary) and Neurohypophysis (posterior pituitary) release of hormones produced in the hypothalamus, and regulating Hunger, Autonomic nervous system, Temperature, and Sexual urges (TAN HATS).<br>Inputs (areas not protected by blood-brain barrier): OVLT (senses change in osmolarity), area postrema (found in dorsal medulla, responds to emetics). | |
| **Lateral nucleus** | Hunger. Destruction → anorexia, failure to thrive (infants). Stimulated by ghrelin, inhibited by leptin. | Lateral injury makes you lean. |
| **Ventromedial nucleus** | Satiety. Destruction (eg, craniopharyngioma) → hyperphagia. Stimulated by leptin. | Ventromedial injury makes you very massive. |
| **Anterior nucleus** | Cooling, parasympathetic. | A/C = Anterior Cooling. |
| **Posterior nucleus** | Heating, sympathetic. | Heating controlled by posterior nucleus ("hot pot"). |
| **Suprachiasmatic nucleus** | Circadian rhythm. | SCN is a Sun-Censing Nucleus. |
| **Supraoptic and paraventricular nuclei** | Synthesize ADH and oxytocin. | SAD POX: Supraoptic = ADH, Paraventricular = OXytocin.<br>ADH and oxytocin are carried by neurophysins down axons to posterior pituitary, where these hormones are stored and released. |
| **Preoptic nucleus** | Thermoregulation, sexual behavior. Releases GnRH. | Failure of GnRH-producing neurons to migrate from olfactory pit → Kallmann syndrome. |

**Thalamus** Major relay for all ascending sensory information except olfaction.

| NUCLEI | INPUT | SENSES | DESTINATION | MNEMONIC |
|---|---|---|---|---|
| **Ventral postero-lateral nucleus** | Spinothalamic and dorsal columns/medial lemniscus | Vibration, pain, pressure, proprioception (conscious), light touch, temperature | 1° somatosensory cortex (parietal lobe) | |
| **Ventral postero-medial nucleus** | Trigeminal and gustatory pathway | Face sensation, taste | 1° somatosensory cortex (parietal lobe) | Very pretty makeup goes on the face |
| **Lateral geniculate nucleus** | CN II, optic chiasm, optic tract | Vision | 1° visual cortex (occipital lobe) | Lateral = light |
| **Medial geniculate nucleus** | Superior olive and inferior colliculus of tectum | Hearing | 1° auditory cortex (temporal lobe) | Medial = music |
| **Ventral anterior and lateral nuclei** | Basal ganglia, cerebellum | Motor | Motor cortices (frontal lobe) | Venus astronauts love to move |

## Limbic system




Collection of neural structures involved in emotion, long-term memory, olfaction, behavior modulation, ANS function.

Consists of hippocampus (red arrows in A), amygdalae, mammillary bodies, anterior thalamic nuclei, cingulate gyrus (yellow arrows in A), entorhinal cortex. Responsible for **f**eeding, **f**leeing, **f**ighting, **f**eeling, and **s**ex.

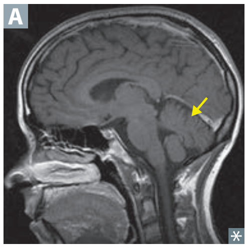
The famous **5 F**'s.

## Dopaminergic pathways

Commonly altered by drugs (eg, antipsychotics) and movement disorders (eg, Parkinson disease).

| PATHWAY | SYMPTOMS OF ALTERED ACTIVITY | NOTES |
|---|---|---|
| **Mesocortical** | ↓ activity → "negative" symptoms (eg, anergia, apathy, lack of spontaneity) | Antipsychotic drugs have limited effect |
| **Mesolimbic** | ↑ activity → "positive" symptoms (eg, delusions, hallucinations) | 1° therapeutic target of antipsychotic drugs → ↓ positive symptoms (eg, in schizophrenia) |
| **Nigrostriatal** | ↓ activity → extrapyramidal symptoms (eg, dystonia, akathisia, parkinsonism, tardive dyskinesia) | Major dopaminergic pathway in brain<br>Significantly affected by movement disorders and antipsychotic drugs |
| **Tuberoinfundibular** | ↓ activity → ↑ prolactin → ↓ libido, sexual dysfunction, galactorrhea, gynecomastia (in males) | |

## Cerebellum




Modulates movement; aids in coordination and balance A.

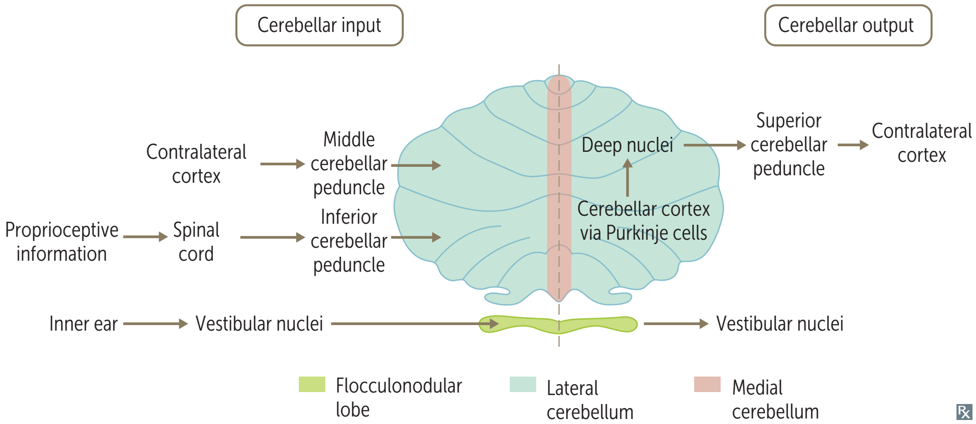
- Ipsilateral (unconscious) proprioceptive information via inferior cerebellar peduncle from spinal cord
- Deep nuclei (lateral → medial)—**d**entate, **e**mboliform, **g**lobose, **f**astigial

**Lateral** lesions—affect voluntary movement of extremities (**lateral** structures); when injured, propensity to fall toward injured (ipsilateral) side.

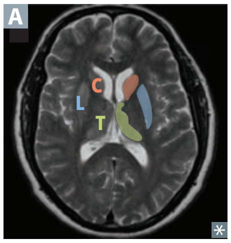
**Medial** lesions (eg, vermis, fastigial nuclei, flocculonodular lobe)—truncal ataxia (wide-based cerebellar gait), nystagmus, head tilting. Generally result in bilateral motor deficits affecting axial and proximal limb musculature (**medial structures**).

**Tests: finger-to-nose**, gait, heel-to-shin, dysdiadochokinesis.

**D**on't **e**at **g**reasy **f**oods.



## Basal ganglia

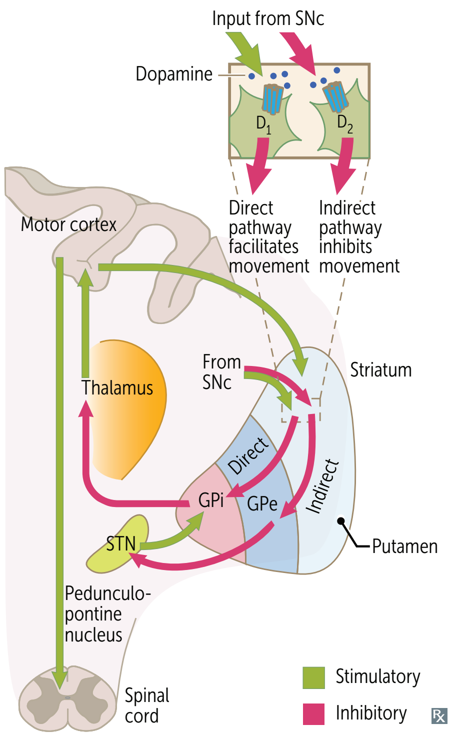


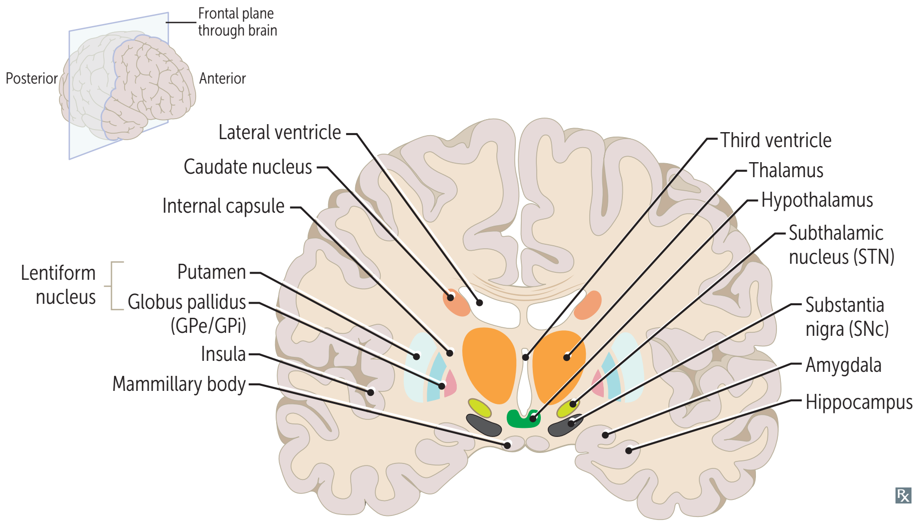

Important in voluntary movements and adjusting posture A.
Receives cortical input, provides negative feedback to cortex to modulate movement.
Striatum = putamen (motor) + Caudate (cognitive).
Lentiform = putamen + globus pallidus.

Direct (excitatory) pathway—SNc input to the striatum via the nigrostriatal dopaminergic pathway releases GABA, which inhibits GABA release from the GPi, disinhibiting the Thalamus via the GPi (↑ motion).
Indirect (inhibitory) pathway—SNc input to the striatum via the nigrostriatal dopaminergic pathway releases GABA that disinhibits STN via GPe inhibition, and STN stimulates GPi to inhibit the thalamus (↓ motion).

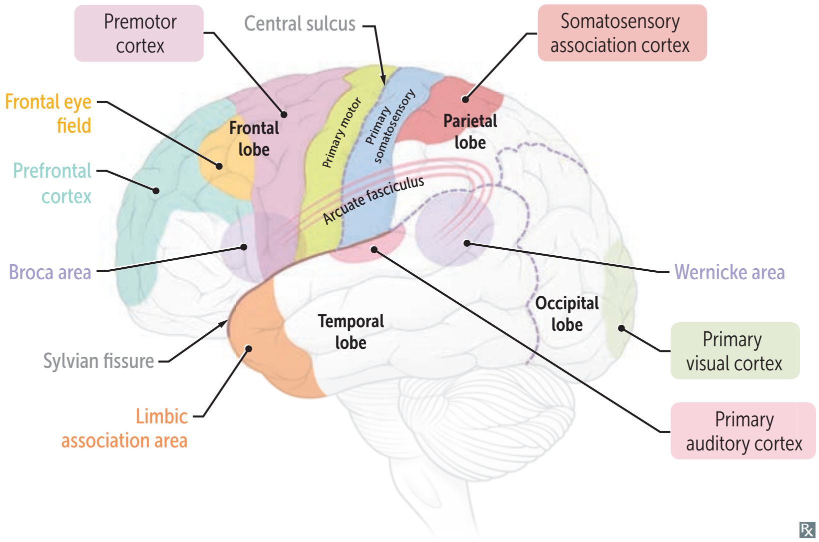
Dopamine binds to $D_1$, stimulating the excitatory pathway, and to $D_2$, inhibiting the inhibitory pathway → ↑ motion.

**$D_1$ Receptor = D1Rect pathway.**
**Indirect ($D_2$) = Inhibitory.**



## Cerebral cortex regions




## Cerebral perfusion

Relies on tight autoregulation. Primarily driven by $P_{CO_2}$ ($P_{O_2}$ also modulates perfusion in severe hypoxia).

Also relies on a pressure gradient between mean arterial pressure (MAP) and intracranial pressure (ICP). ↓ blood pressure or ↑ ICP → ↓ cerebral perfusion pressure (CPP).

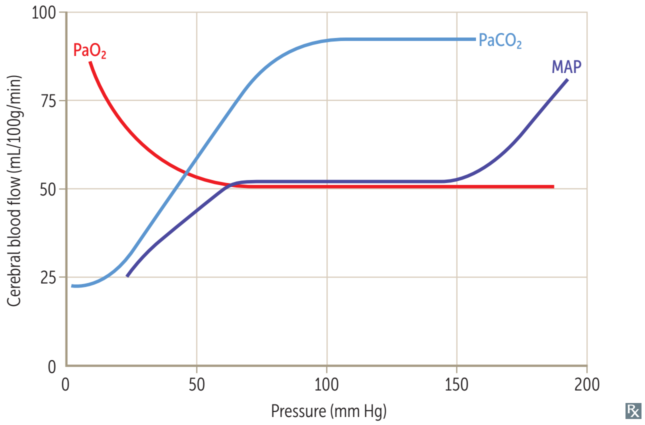
Cushing reflex—triad of hypertension, bradycardia, and respiratory depression in response to ↑ ICP.

Therapeutic hyperventilation → ↓ $P_{CO_2}$ → vasoconstriction → ↓ cerebral blood flow → ↓ ICP. May be used to treat acute cerebral edema (eg, 2° to stroke) unresponsive to other interventions.

CPP = MAP – ICP. If CPP = 0, there is no cerebral perfusion → brain death.

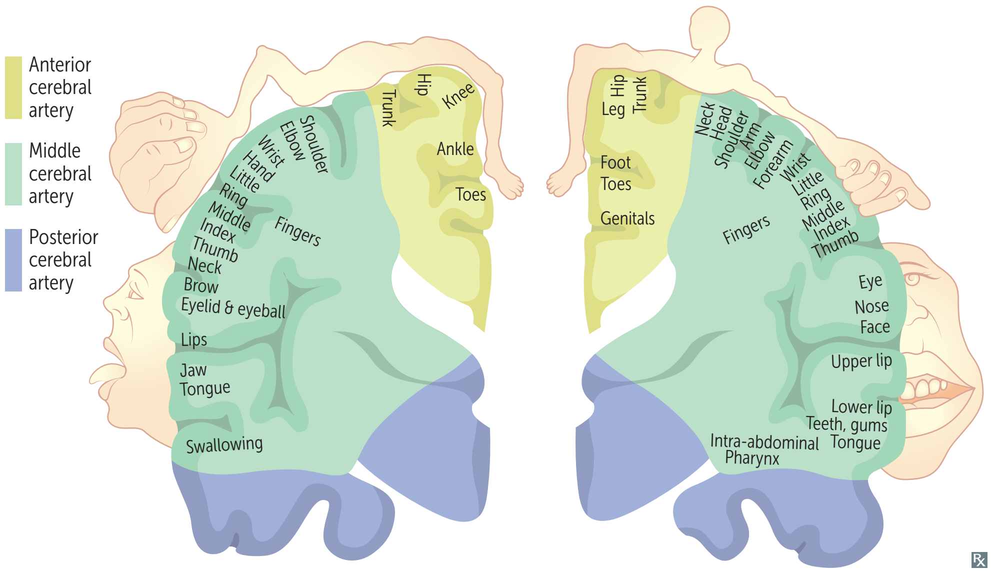
Hypoxemia increases CPP only if $P_{O_2}$ < 50 mm Hg.

CPP is directly proportional to $P_{CO_2}$ until $P_{CO_2}$ > 90 mm Hg.

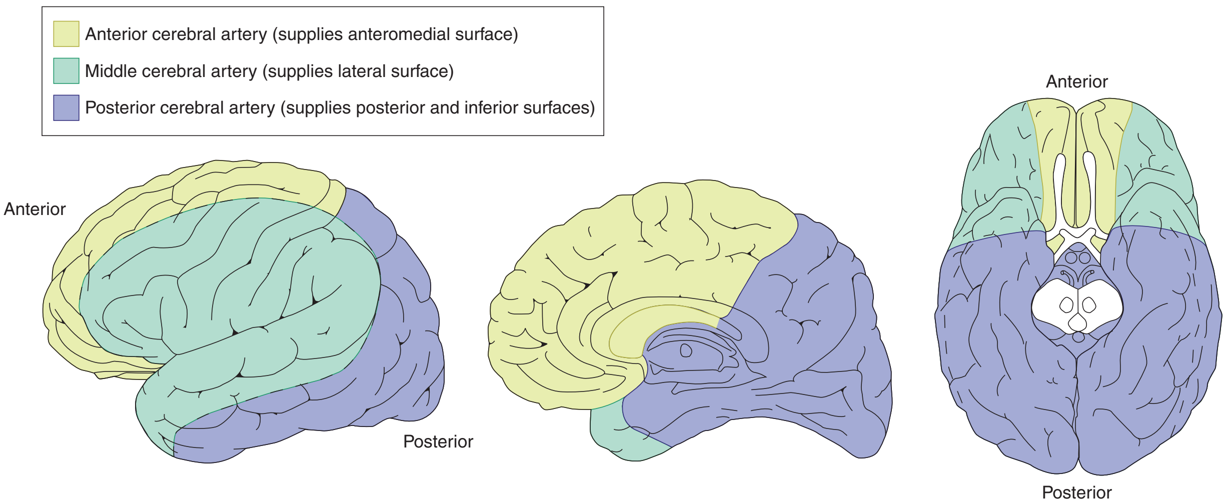


## Homunculus

Topographic representation of motor and sensory areas in the cerebral cortex. Distorted appearance is due to certain body regions being more richly innervated and thus having ↑ cortical representation.




## Cerebral arteries—cortical distribution




## Watershed zones


Cortical border zones occur between anterior and middle cerebral arteries and posterior and middle cerebral arteries (blue areas in A).

Internal border zones occur between the superficial and deep vascular territories of the middle cerebral artery (red areas in A).

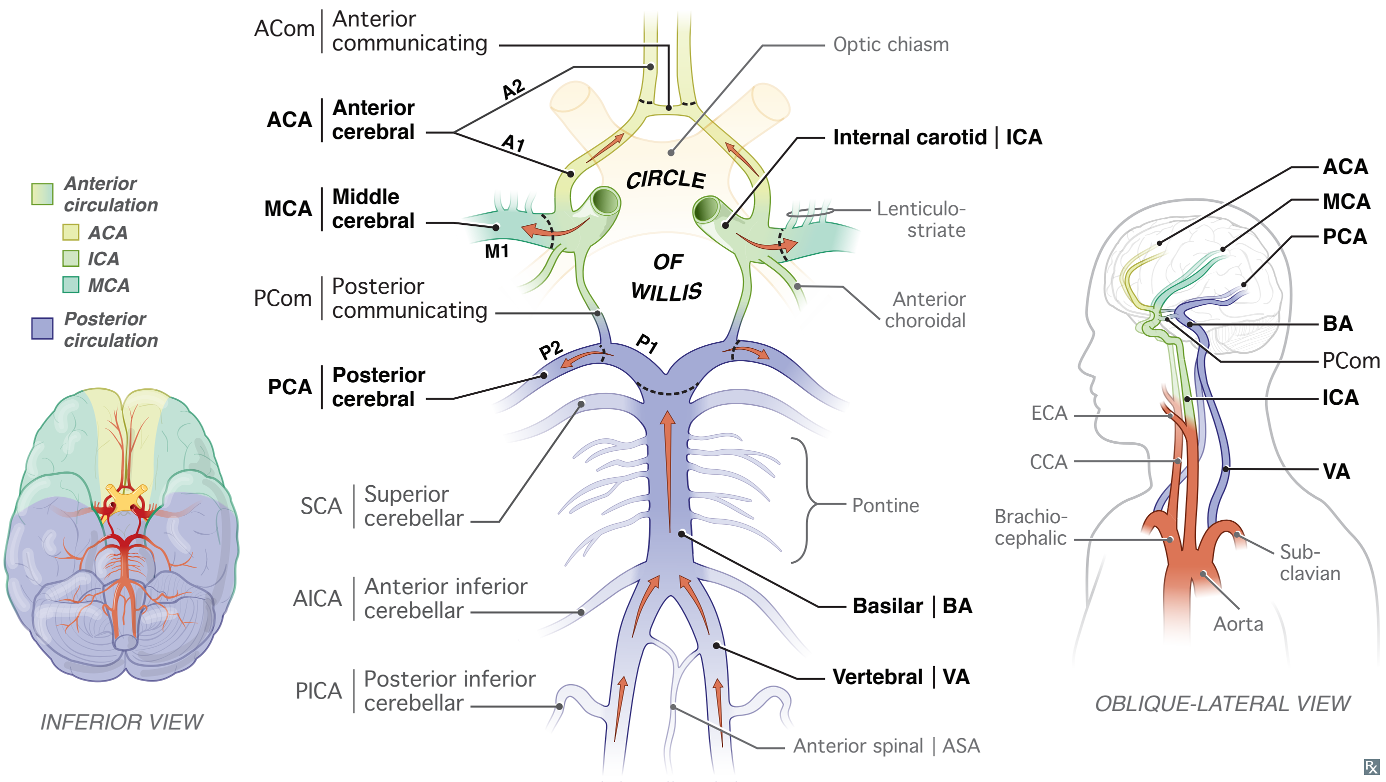
Common locations for brain metastases.

Infarct due to severe hypoperfusion:

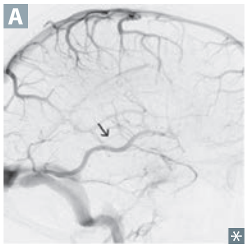
- ACA-MCA watershed infarct—proximal upper and lower extremity weakness ("man-in-a-barrel syndrome").
- PCA-MCA watershed infarct—higher-order visual dysfunction.

## Circle of Willis

System of anastomoses between anterior and posterior blood supplies to brain.

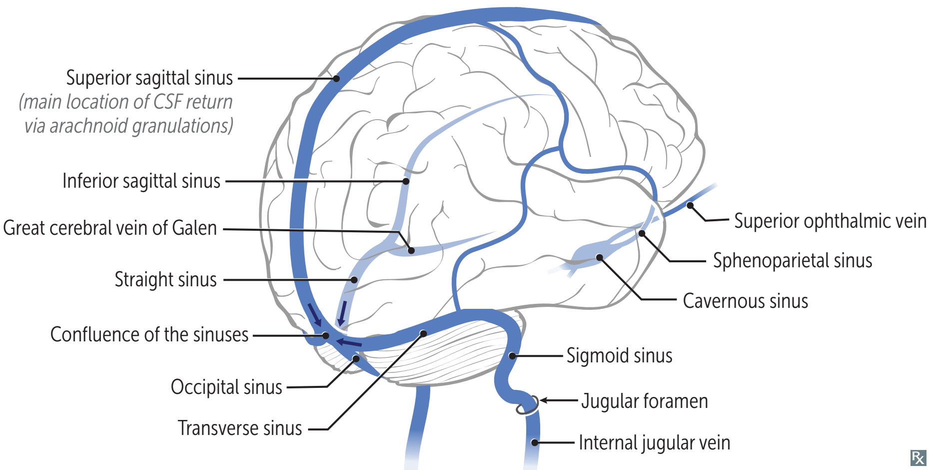



## Dural venous sinuses

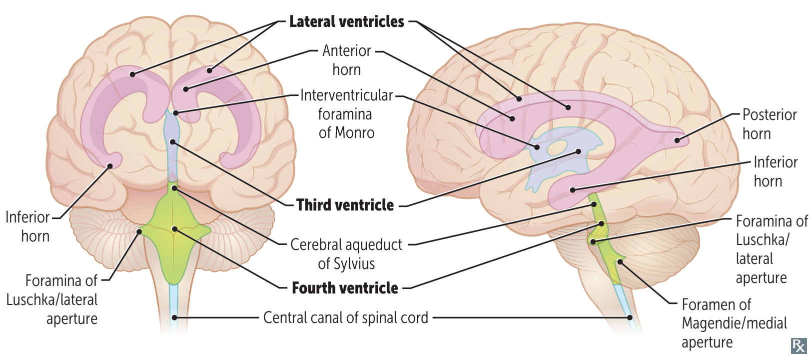



Large venous channels A that run through the periosteal and meningeal layers of the dura mater. Drain blood from cerebral veins (arrow) and receive CSF from arachnoid granulations. Empty into internal jugular vein.

**Venous sinus thrombosis**—presents with signs/symptoms of ↑ ICP (eg, headache, seizures, papilledema, focal neurologic deficits). May lead to venous hemorrhage. Associated with hypercoagulable states (eg, pregnancy, OCP use, factor V Leiden).



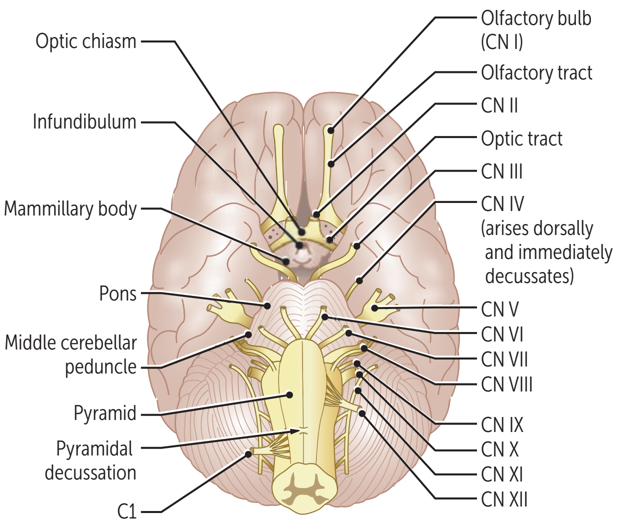
## Ventricular system




Lateral ventricles → 3rd ventricle via right and left interventricular foramina of Monro.
3rd ventricle → 4th ventricle via cerebral aqueduct of Sylvius.
4th ventricle → subarachnoid space via:
- Foramina of **L**uschka = **l**ateral.
- Foramen of **M**agendie = **m**edial.

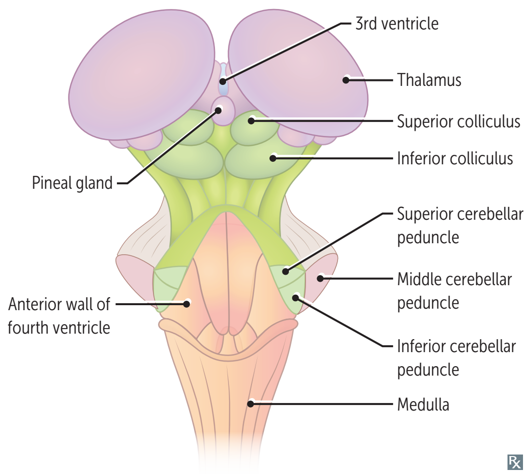
CSF made by choroid plexuses located in the lateral and fourth ventricles. Travels to subarachnoid space via foramina of Luschka and Magendie, is reabsorbed by arachnoid granulations, and then drains into dural venous sinuses.

## Brain stem—ventral view




**4** CN are above pons (I, II, III, IV).
**4** CN exit the pons (V, VI, VII, VIII).
**4** CN are in medulla (IX, X, XI, XII).
**4** CN nuclei are medial (III, IV, VI, XII).
"Factors of 12, except 1 and 2."

## Brain stem—dorsal view (cerebellum removed)



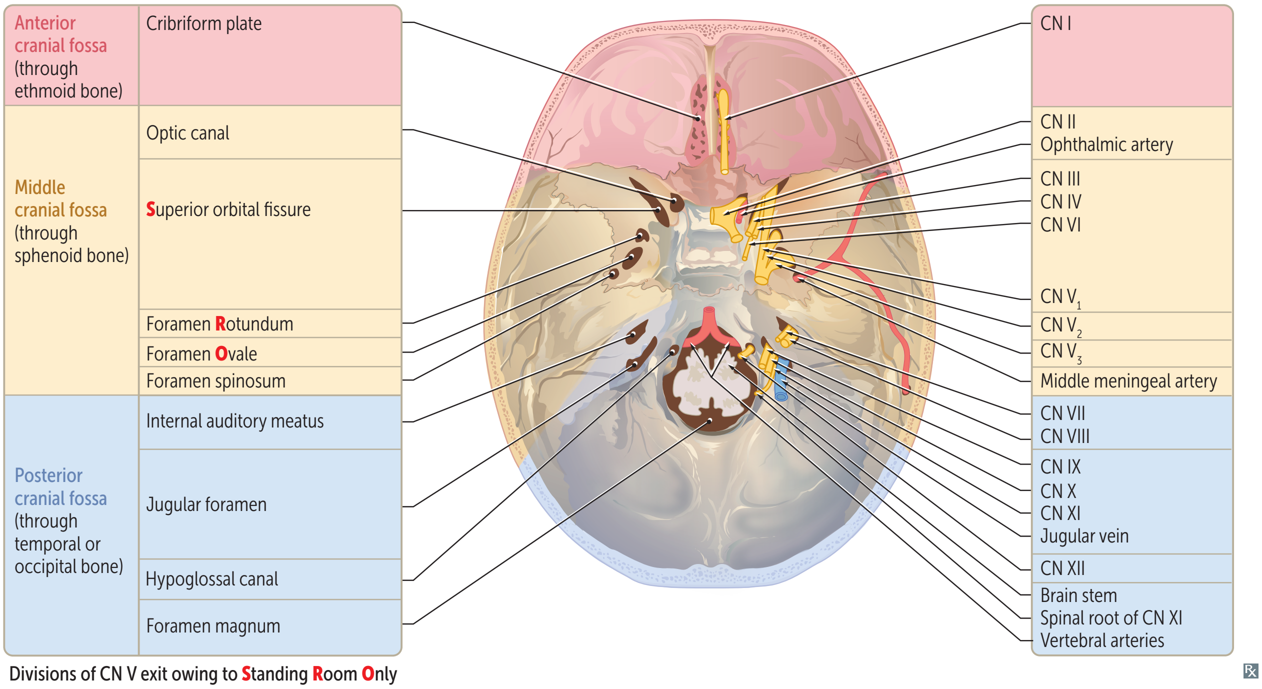

Pineal gland—melatonin secretion, circadian rhythms.
Superior colliculi—direct eye movements to stimuli (noise/movements) or objects of interest.
Inferior colliculi—auditory.
Your eyes are **above** your ears, and the superior colliculus (visual) is **above** the inferior colliculus (auditory).

| | | |
|---|---|---|
| **Cranial nerve nuclei** | Located in tegmentum portion of brain stem (between dorsal and ventral portions):<br>▪ Midbrain—nuclei of CN III, IV<br>▪ Pons—nuclei of CN V, VI, VII, VIII<br>▪ Medulla—nuclei of CN IX, X, XII<br>▪ Spinal cord—nucleus of CN XI | **L**ateral nuclei = sensory (a**l**ar plate).<br>—Sulcus limitans—<br>**M**edial nuclei = **m**otor (basal plate). |

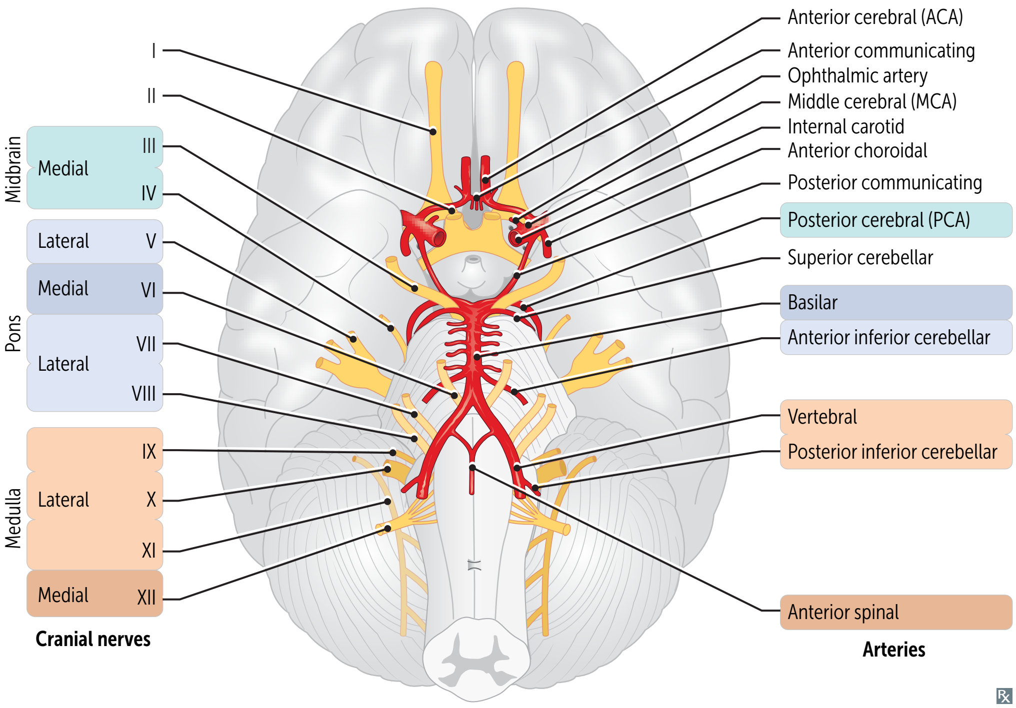
## Vagal nuclei

| NUCLEUS | FUNCTION | CRANIAL NERVES |
|---|---|---|
| **Nucleus tractus solitarius** | Visceral **s**ensory information (eg, taste, baroreceptors, gut distention)<br>May play a role in vomiting | VII, IX, X |
| **Nucleus ambiguus** | **M**otor innervation of pharynx, larynx, upper esophagus (eg, swallowing, palate elevation) | IX, X, XI (cranial portion) |
| **Dorsal motor nucleus** | Sends autonomic (parasympathetic) fibers to heart, lungs, upper GI | X |

## Cranial nerves and vessel pathways




## Cranial nerves and arteries



## Cranial nerves

| NERVE | CN | FUNCTION | TYPE | MNEMONIC |
|---|---|---|---|---|
| **Olfactory** | I | Smell (only CN without thalamic relay to cortex) | Sensory | Some |
| **Optic** | II | Sight | Sensory | Say |
| **Oculomotor** | III | Eye movement (SR, IR, MR, IO), pupillary constriction (sphincter pupillae: pretectal nucleus, Edinger-Westphal nuclei, muscarinic receptors), accommodation, eyelid opening (levator palpebrae) | Motor | Marry |
| **Trochlear** | IV | Eye movement (SO) | Motor | Money |
| **Trigeminal** | V | Mastication, facial sensation (ophthalmic, maxillary, mandibular divisions), somatosensation from anterior 2/3 of tongue, dampening of loud noises (tensor tympani) | Both | But |
| **Abducens** | VI | Eye movement (LR) | Motor | My |
| **Facial** | VII | Facial movement, taste from anterior 2/3 of tongue (chorda tympani), lacrimation, salivation (submandibular and sublingual glands are innervated by CN seven), eye closing (orbicularis oculi), auditory volume modulation (stapedius) | Both | Brother |
| **Vestibulocochlear** | VIII | Hearing, balance | Sensory | Says |
| **Glossopharyngeal** | IX | Taste and sensation from posterior 1/3 of tongue, swallowing, salivation (parotid gland), monitoring carotid body and sinus chemo- and baroreceptors, and elevation of pharynx/larynx (stylopharyngeus) | Both | Big |
| **Vagus** | X | Taste from supraglottic region, swallowing, soft palate elevation, midline uvula, talking, cough reflex, parasympathetics to thoracoabdominal viscera, monitoring aortic arch chemo- and baroreceptors | Both | Brains |
| **Accessory** | XI | Head turning, shoulder shrugging (SCM, trapezius) | Motor | Matter |
| **Hypoglossal** | XII | Tongue movement | Motor | Most |

## Cranial nerve reflexes

| REFLEX | AFFERENT | EFFERENT |
|---|---|---|
| **Corneal** | $V_1$ ophthalmic (nasociliary branch) | Bilateral VII (temporal branch—orbicularis oculi) |
| **Cough** | X | X (also phrenic and spinal nerves) |
| **Gag** | IX | X |
| **Jaw jerk** | $V_3$ (sensory—muscle spindle from masseter) | $V_3$ (motor—masseter) |
| **Lacrimation** | $V_1$ (loss of reflex does not preclude emotional tears) | VII |
| **Pupillary** | II | III |

**Mastication muscles**

3 muscles close jaw: **m**asseter, te**m**poralis, **m**edial pterygoid. Lateral pterygoids protrude the jaw. All are innervated by trigeminal nerve ($V_3$).

**M**'s **m**unch.

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**Spinal nerves**

There are 31 pairs of spinal nerves: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal.
Nerves C1–C7 exit above the corresponding vertebrae (eg, C3 exits above the 3rd cervical vertebra). C8 spinal nerve exits below C7 and above T1. All other nerves exit below (eg, L2 exits below the 2nd lumbar vertebra).

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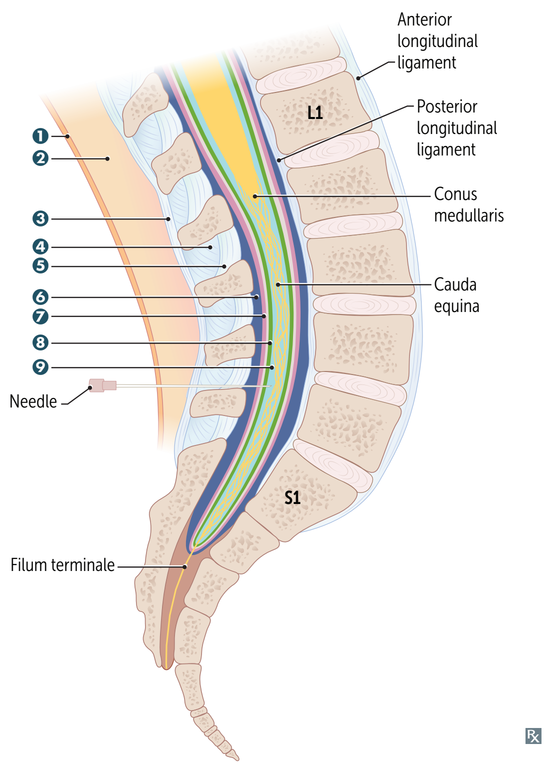
**Spinal cord—lower extent**

In adults, spinal cord ends at lower border of L1–L2 vertebrae. **S**ubarachnoid **s**pace (which contains the CSF) extends to lower border of **S2** vertebra. Lumbar puncture is usually performed between L3–L4 or L4–L5 (level of cauda equina).

Goal of lumbar puncture is to obtain sample of CSF without damaging spinal cord. To **keep** the cord **alive**, keep the spinal needle between **L3** and **L5**.

Needle passes through:

1. skin
2. fascia and fat
3. supraspinous ligament
4. interspinous ligament
5. ligamentum flavum
6. epidural space (epidural anesthesia needle stops here)
7. dura mater
8. arachnoid mater
9. subarachnoid space (CSF collection occurs here)

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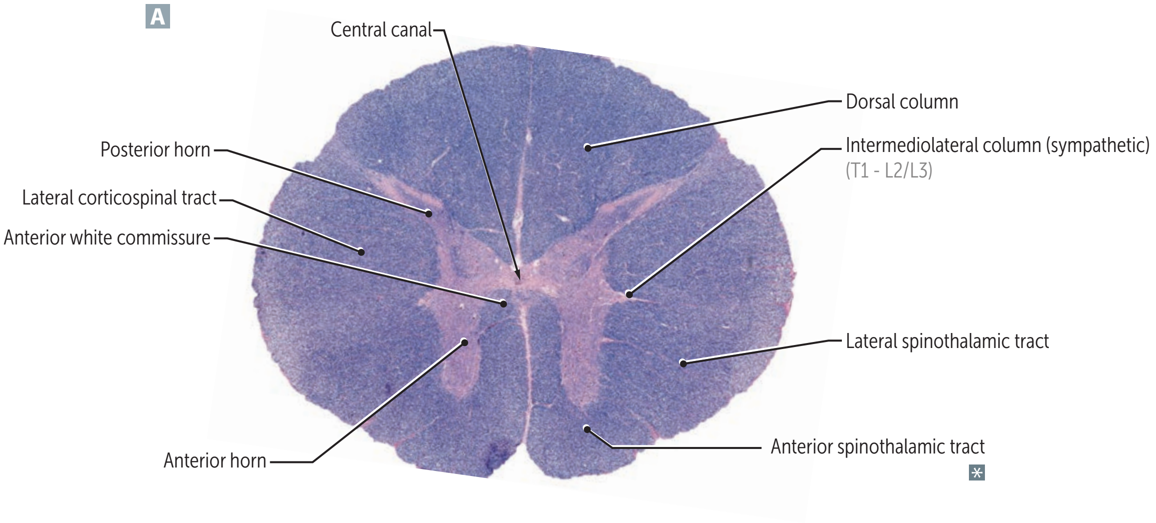
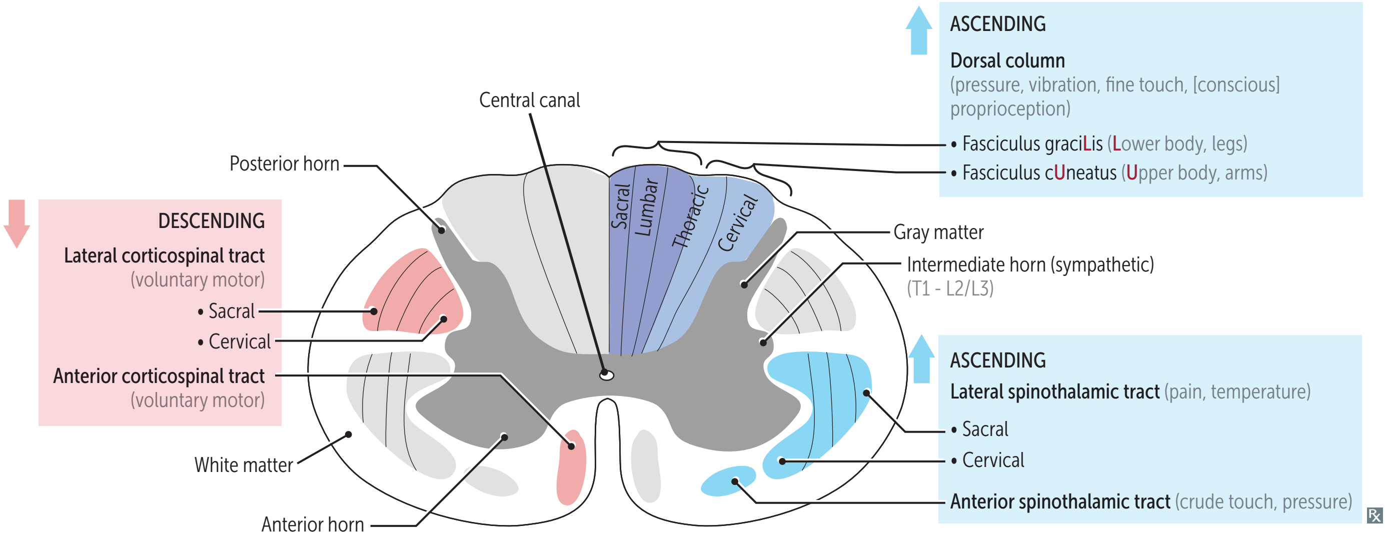
**Spinal cord and associated tracts**

Legs (lumbosacral) are lateral in lateral corticospinal, spinothalamic tracts. Thoracic spinal cord section in A.

Dorsal columns are organized as you are, with hands at sides. "Arms outside, legs inside."

A



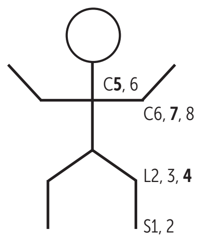



**Spinal tract anatomy and functions**

Ascending tracts synapse and then cross.

| TRACT | FUNCTION | 1ST-ORDER NEURON | SYNAPSE 1 | 2ND-ORDER NEURON | SYNAPSE 2 + PROJECTIONS |
|---|---|---|---|---|---|
| **Ascending tracts** | | | | | |
| **Dorsal column** | Pressure, vibration, fine touch, (conscious) proprioception | Sensory nerve ending → bypasses pseudounipolar cell body in dorsal root ganglion → enters spinal cord → ascends ipsilaterally in dorsal columns | Nucleus gracilis, nucleus cuneatus (ipsilateral medulla) | Decussates in medulla → ascends contralaterally as the medial lemniscus | VPL (thalamus) → sensory cortex |
| **Spinothalamic tract** | Lateral: pain, temperature<br>Anterior: crude touch, pressure | Sensory nerve ending (Aδ and C fibers) → bypasses pseudounipolar cell body in dorsal root ganglion → enters spinal cord | Ipsilateral gray matter (spinal cord) | Decussates in spinal cord as the anterior white commissure → ascends contralaterally | |
| **Descending tract** | | | | | |
| **Lateral corticospinal tract** | Voluntary movement of contralateral limbs | UMN: cell body in 1° motor cortex → descends ipsilaterally (through posterior limb of internal capsule and cerebral peduncle), most fibers decussate at caudal medulla (pyramidal decussation) → descends contralaterally | Cell body of anterior horn (spinal cord) | LMN: leaves spinal cord | NMJ → muscle fibers |

### Clinical reflexes




Reflexes count up in order (main nerve root in **bold**):

- **Achilles reflex** = **S1**, S2 ("buckle my shoe")
- **Patellar reflex** = L2-**L4** ("kick the door")
- **Biceps and brachioradialis reflexes** = **C5**, C6 ("pick up sticks")
- **Triceps reflex** = C6, **C7**, C8 ("lay them straight")

Additional reflexes:

- **Cremasteric reflex** = L1, L2 ("testicles move")
- **Anal wink reflex** = S3, S4 ("winks galore")

Reflex grading:

- 0: absent
- 1: hypoactive
- 2: normal
- 3: hyperactive
- 4: clonus

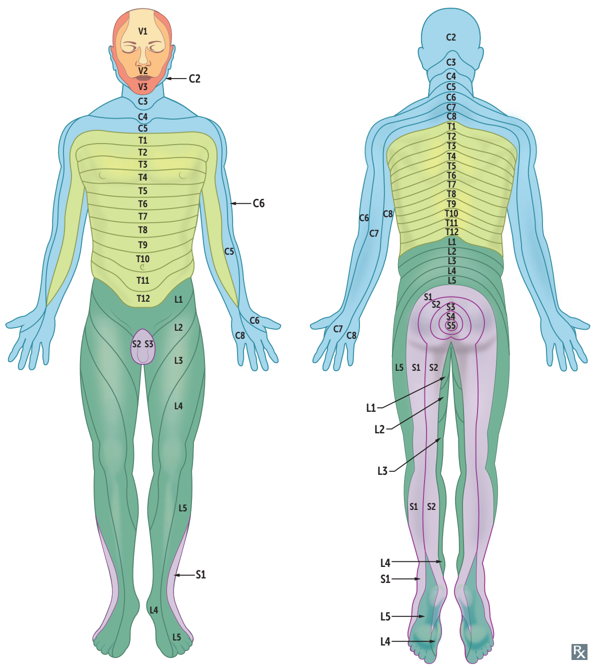
### Primitive reflexes

CNS reflexes that are present in a healthy infant, but are absent in a neurologically intact adult. Normally disappear within 1st year of life. These primitive reflexes are inhibited by a mature/developing frontal lobe. They may reemerge in adults following frontal lobe lesions → loss of inhibition of these reflexes.

| | |
|---|---|
| **Moro reflex** | "Hang on for life" reflex—abduct/extend arms when startled, and then draw together. |
| **Rooting reflex** | Movement of head toward one side if cheek or mouth is stroked (nipple seeking). |
| **Sucking reflex** | Sucking response when roof of mouth is touched. |
| **Palmar reflex** | Curling of fingers if palm is stroked. |
| **Plantar reflex** | Dorsiflexion of large toe and fanning of other toes with plantar stimulation.<br>Babinski sign—presence of this reflex in an adult, which may signify a UMN lesion. |
| **Galant reflex** | Stroking along one side of the spine while newborn is in ventral suspension (face down) causes lateral flexion of lower body toward stimulated side. |

### Landmark dermatomes

| DERMATOME | CHARACTERISTICS |
|---|---|
| C2 | Posterior half of skull |
| C3 | High turtleneck shirt<br>Diaphragm and gallbladder pain referred to the right shoulder via phrenic nerve<br>C3, 4, 5 keeps the diaphragm alive |
| C4 | Low-collar shirt |
| C6 | Includes thumbs<br>Thumbs up sign on left hand looks like a 6 |
| T4 | At the nipple<br>T4 at the teat pore |
| T7 | At the xiphoid process<br>7 letters in xiphoid |
| T10 | At the umbilicus (belly butten)<br>Point of referred pain in early appendicitis |
| L1 | At the Inguinal Ligament |
| L4 | Includes the kneecaps<br>Down on ALL 4's |
| S2, S3, S4 | Sensation of penile and anal zones<br>S2, 3, 4 keep the penis off the floor |



## ▸ NEUROLOGY—PATHOLOGY

### Common brain lesions

| AREA OF LESION | CONSEQUENCE | EXAMPLES/COMMENTS |
|---|---|---|
| **Frontal lobe** | Disinhibition and deficits in concentration, orientation, judgment; may have reemergence of primitive reflexes | |
| **Frontal eye fields** | Destructive lesions (eg, MCA stroke): eyes look toward brain lesion (ie, away from side of hemiplegia) | |
| **Paramedian pontine reticular formation** | Eyes look away from brain lesion (ie, toward side of hemiplegia) | |
| **Medial longitudinal fasciculus** | Internuclear ophthalmoplegia (impaired adduction of ipsilateral eye; nystagmus of contralateral eye with abduction) | Multiple sclerosis |
| **Dominant parietal cortex** | Agraphia, acalculia, finger agnosia, left-right disorientation | Gerstmann syndrome |
| **Nondominant parietal cortex** | Agnosia of the contralateral side of the world | Hemispatial neglect syndrome |
| **Hippocampus (bilateral)** | Anterograde amnesia—inability to make new memories | |
| **Basal ganglia** | May result in tremor at rest, chorea, athetosis | Parkinson disease, Huntington disease, Wilson disease |
| **Subthalamic nucleus** | Contralateral hemiballismus | |
| **Mammillary bodies (bilateral)** | Wernicke-Korsakoff syndrome—Confusion, Ataxia, Nystagmus, Ophthalmoplegia, memory loss (anterograde and retrograde amnesia), confabulation, personality changes | Wernicke problems come in a CAN O' beer and other conditions associated with thiamine deficiency |
| **Amygdala (bilateral)** | Klüver-Bucy syndrome—disinhibited behavior (eg, hyperphagia, hypersexuality, hyperorality) | HSV-1 encephalitis |
| **Dorsal midbrain** | Parinaud syndrome—vertical gaze palsy, pupillary light-near dissociation, lid retraction, convergence-retraction nystagmus | Stroke, hydrocephalus, pinealoma |
| **Reticular activating system (midbrain)** | Reduced levels of arousal and wakefulness | Coma |
| **Cerebellar hemisphere** | Intention tremor, limb ataxia, loss of balance; damage to cerebellum → ipsilateral deficits; fall toward side of lesion | Cerebellar hemispheres are laterally located—affect lateral limbs |
| **Cerebellar vermis** | Truncal ataxia (wide-based, "drunken sailor" gait), nystagmus | Vermis is centrally located—affects central body<br>Degeneration associated with chronic alcohol use |
| **Red nucleus (midbrain)** | Decorticate (flexor) posturing—lesion above red nucleus, presents with flexion of upper extremities and extension of lower extremities<br>Decerebrate (extensor) posturing—lesion at or below red nucleus, presents with extension of upper and lower extremities | Worse prognosis with decerebrate posturing<br>In decorticate posturing, your hands are near the cor (heart) |

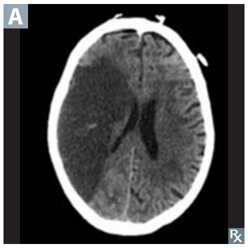
**Ischemic brain disease/stroke**

Irreversible neuronal injury begins after 5 minutes of hypoxia. Most **vulnerable**: **hippo**campus, **n**eocortex, cerebellum (**Pur**kinje cells), **water**shed areas ("**vulnerable hippos** **n**eed **pure water**").

Stroke imaging: noncontrast CT to exclude hemorrhage (before tPA can be given). CT detects ischemic changes in 6–24 hr. Diffusion-weighted MRI can detect ischemia within 3–30 min.

| TIME SINCE ISCHEMIC EVENT | 12–24 HOURS | 24–72 HOURS | 3–5 DAYS | 1–2 WEEKS | > 2 WEEKS |
|---|---|---|---|---|---|
| Histologic features | Eosinophilic cytoplasm + pyknotic nuclei (red neurons) | Necrosis + neutrophils | Macrophages (microglia) | Reactive gliosis (astrocytes) + vascular proliferation | Glial scar |

**Ischemic stroke**



Acute blockage of vessels → disruption of blood flow and subsequent ischemia → infarction → liquefactive necrosis.

3 types:

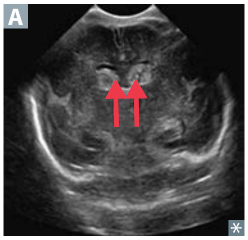
- Thrombotic—due to a clot forming directly at site of infarction (commonly the MCA A), usually over a ruptured atherosclerotic plaque.
- Embolic—embolus from another part of the body obstructs vessel. Can affect multiple vascular territories. Examples: atrial fibrillation, carotid artery stenosis, DVT with patent foramen ovale (paradoxical embolism), infective endocarditis.
- Hypoxic—due to hypoperfusion or hypoxemia. Common during cardiovascular surgeries, tends to affect watershed areas.

Treatment: tPA (if within 3–4.5 hr of onset and no hemorrhage/risk of hemorrhage) and/or thrombectomy (if large artery occlusion). Reduce risk with medical therapy (eg, aspirin, clopidogrel); optimum control of blood pressure, blood sugars, lipids; smoking cessation; and treat conditions that ↑ risk (eg, atrial fibrillation, carotid artery stenosis).

**Transient ischemic attack**

Brief, reversible episode of focal neurologic dysfunction without acute infarction (⊖ MRI), with the majority resolving in < 15 minutes; ischemia (eg, embolus, small vessel stenosis). May present with amaurosis fugax (transient visual loss) due to retinal artery emboli from carotid artery disease.

**Neonatal intraventricular hemorrhage**




Bleeding into ventricles (arrows in A show blood in intraventricular spaces on ultrasound). Increased risk in premature and low-birth-weight infants. Originates in germinal matrix, a highly vascularized layer within the subventricular zone. Due to reduced glial fiber support and impaired autoregulation of BP in premature infants. Can present with altered level of consciousness, bulging fontanelle, hypotension, seizures, coma.

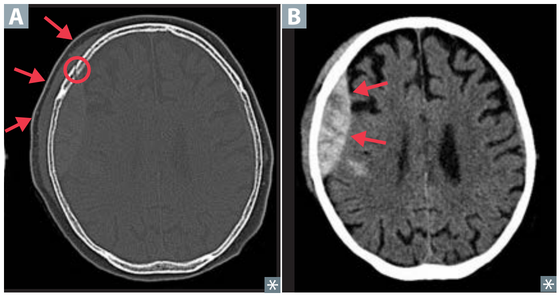
## Intracranial hemorrhage

### Epidural hematoma

Rupture of middle meningeal artery (branch of maxillary artery), often 2° to skull fracture (circle in A) involving the pterion (thinnest area of the lateral skull). Might present with transient loss of consciousness → recovery ("lucid interval") → rapid deterioration due to hematoma expansion.

Scalp hematoma (arrows in A) and rapid intracranial expansion (arrows in B) under systemic arterial pressure → transtentorial herniation, CN III palsy.

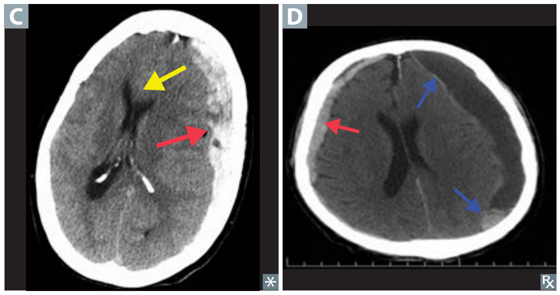
CT shows biconvex (lentiform), hyperdense blood collection B **not crossing suture lines**.




### Subdural hematoma

Rupture of bridging veins. Can be acute (traumatic, high-energy impact → hyperdense on CT) or chronic (associated with mild trauma, cerebral atrophy, elderly, chronic alcohol overuse → hypodense on CT). Also seen in shaken babies. Predisposing factors: brain atrophy, trauma.

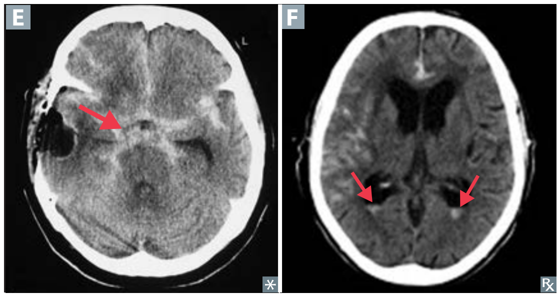
Crescent-shaped hemorrhage (red arrows in C and D) that **crosses suture lines**. Can cause midline shift (yellow arrow in C), findings of "acute on chronic" hemorrhage (blue arrows in D).




### Subarachnoid hemorrhage

Bleeding E F due to trauma, or rupture of an aneurysm (such as a saccular aneurysm E) or arteriovenous malformation. Rapid time course. Patients complain of "worst headache of my life." Bloody or yellow (xanthochromic) lumbar puncture.

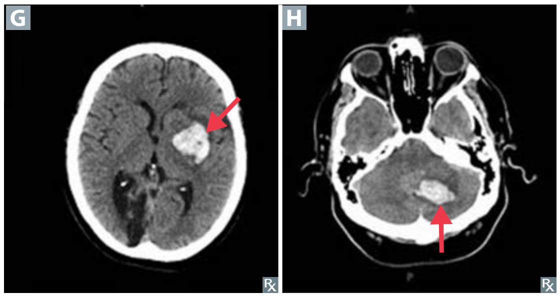
Vasospasm can occur due to blood breakdown or rebleed 3–10 days after hemorrhage → ischemic infarct; nimodipine used to prevent/reduce vasospasm. ↑ risk of developing communicating and/or obstructive hydrocephalus.




### Intraparenchymal hemorrhage

Most commonly caused by systemic hypertension. Also seen with amyloid angiopathy (recurrent lobar hemorrhagic stroke in elderly), vascular malformations, vasculitis, neoplasm. May be 2° to reperfusion injury in ischemic stroke.

Hypertensive hemorrhages (Charcot-Bouchard microaneurysm) most often occur in putamen of basal ganglia (lenticulostriate vessels G), followed by thalamus, pons, and cerebellum H.

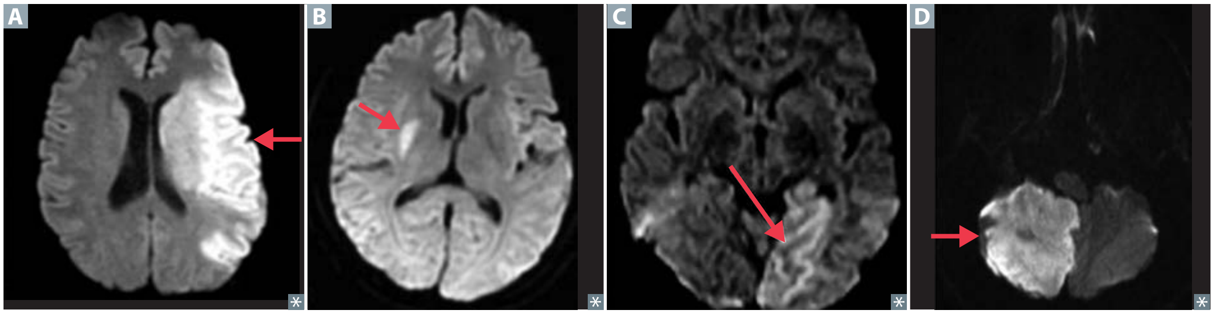


### Effects of strokes

| ARTERY | AREA OF LESION | SYMPTOMS | NOTES |
|---|---|---|---|
| **Anterior circulation** | | | |
| **Anterior cerebral artery** | Motor and sensory cortices—lower limb. | Contralateral paralysis and sensory loss—lower limb, urinary incontinence. | |
| **Middle cerebral artery** | Motor and sensory cortices A—upper limb and face.<br>Temporal lobe (Wernicke area); frontal lobe (Broca area). | Contralateral paralysis and sensory loss—face and upper limb.<br>Aphasia if in dominant (usually left) hemisphere. Hemineglect if lesion affects nondominant (usually right) hemisphere. | Wernicke aphasia is associated with right superior quadrant visual field defect due to temporal lobe involvement. |
| **Lenticulo-striate artery** | Striatum, internal capsule. | Contralateral paralysis. Absence of cortical signs (eg, neglect, aphasia, visual field loss). | Pure motor stroke (most common). Common location of lacunar infarcts B, due to microatheroma and hyaline arteriosclerosis (lipohyalinosis) 2° to unmanaged hypertension. |
| **Posterior circulation** | | | |
| **Posterior cerebral artery** | Occipital lobe C. | Contralateral hemianopia with macular sparing; alexia without agraphia (dominant hemisphere, extending to splenium of corpus callosum); prosopagnosia (nondominant hemisphere). | |
| **Basilar artery** | Pons, medulla, lower midbrain.<br>Corticospinal and corticobulbar tracts.<br>Ocular cranial nerve nuclei, paramedian pontine reticular formation. | If RAS spared, consciousness is preserved.<br>Quadriplegia; loss of voluntary facial, mouth, and tongue movements.<br>Loss of horizontal, but not vertical, eye movements. | Locked-in syndrome (locked in the basement). |
| **Anterior inferior cerebellar artery** | Facial nucleus.<br>Vestibular nuclei.<br>Spinothalamic tract, spinal trigeminal nucleus.<br>Sympathetic fibers.<br>Middle and inferior cerebellar peduncles.<br>Labyrinthine artery. | Paralysis of face (LMN lesion vs UMN lesion in cortical stroke), ↓ lacrimation, ↓ salivation, ↓ taste from anterior 2/3 of tongue.<br>Vomiting, vertigo, nystagmus<br>↓ pain and temperature sensation from contralateral body, ipsilateral face.<br>Ipsilateral Horner syndrome.<br>Ipsilateral ataxia, dysmetria.<br>Ipsilateral sensorineural deafness, vertigo. | Lateral pontine syndrome.<br>Facial nucleus effects are specific to AICA lesions. |

### Effects of strokes *(continued)*

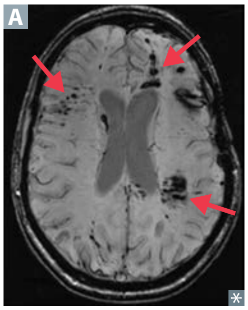
| ARTERY | AREA OF LESION | SYMPTOMS | NOTES |
|---|---|---|---|
| **Posterior inferior cerebellar artery** | Nucleus ambiguus (CN IX, X, XI).<br>Vestibular nuclei.<br>Lateral spinothalamic tract, spinal trigeminal nucleus.<br>Sympathetic fibers.<br>Inferior cerebellar peduncle. | **Dysphagia**, **hoarseness**, ↓ **gag reflex**, hiccups.<br>Vomiting, vertigo, nystagmus<br>↓ pain and temperature sensation from contralateral body, ipsilateral face.<br>Ipsilateral Horner syndrome.<br>Ipsilateral ataxia, dysmetria. | Lateral medullary (Wallenberg) syndrome.<br>Nucleus ambiguus effects are specific to PICA lesions D.<br>"Don't **pick a** (**PICA**) **horse** (hoarseness) that **can't eat** (dysphagia)." |
| **Anterior spinal artery** | Corticospinal tract.<br>Medial lemniscus.<br>Caudal medulla—hypoglossal nerve. | Contralateral paralysis—upper and lower limbs.<br>↓ contralateral proprioception.<br>Ipsilateral hypoglossal dysfunction (tongue deviates ipsilaterally). | Medial Medullary syndrome—caused by infarct of paramedian branches of ASA and/or vertebral arteries. **Ants** love **M&M's**. |




**Central poststroke pain syndrome**

Neuropathic pain due to thalamic lesions. Initial paresthesias followed in weeks to months by allodynia (ordinarily painless stimuli cause pain) and dysesthesia (altered sensation) on the contralateral side. Occurs in 10% of stroke patients.

**Diffuse axonal injury**




Traumatic shearing of white matter tracts during rapid acceleration and/or deceleration of the brain (eg, motor vehicle accident). Usually results in devastating neurologic injury, often causing coma or persistent vegetative state. MRI shows multiple lesions (punctate hemorrhages) involving white matter tracts A.

## Aphasia

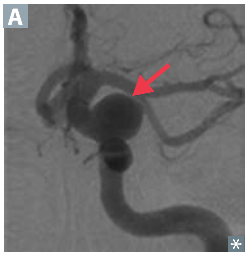
Aphasia—higher-order language deficit (inability to understand/produce/use language appropriately); caused by pathology in dominant cerebral hemisphere (usually left).
Dysarthria—motor inability to produce speech (movement deficit).

| TYPE | COMMENTS |
|---|---|
| **Broca (expressive)** | Broca area in inferior frontal gyrus of frontal lobe. Associated with defective language production. Patients appear frustrated, insight intact.<br>Broca = broken boca (*boca* = mouth in Spanish). |
| **Wernicke (receptive)** | Wernicke area in superior temporal gyrus of temporal lobe. Associated with impaired language comprehension. Patients do not have insight.<br>Wernicke is a word salad and makes no sense. |
| **Conduction** | Can be caused by damage to arCuate fasciculus. |
| **Global** | Broca and Wernicke areas affected. |

## Aneurysms

Abnormal dilation of an artery due to weakening of vessel wall.

### Saccular aneurysm




Also called berry aneurysm A. Occurs at bifurcations in the circle of Willis. Most common site is junction of ACom and ACA. Associated with ADPKD, Ehlers-Danlos syndrome. Other risk factors: advanced age, hypertension, tobacco smoking.
Usually clinically silent until rupture (most common complication) → subarachnoid hemorrhage ("worst headache of my life" or "thunderclap headache") → focal neurologic deficits. Can also cause symptoms via direct compression of surrounding structures by growing aneurysm.

- ACom—compression → bitemporal hemianopia (compression of optic chiasm); visual acuity deficits; rupture → ischemia in ACA distribution → contralateral lower extremity hemiparesis, sensory deficits.
- MCA—rupture → ischemia in MCA distribution → contralateral upper extremity and lower facial hemiparesis, sensory deficits.
- PCom—compression → ipsilateral CN III palsy → mydriasis ("blown pupil"); may also see ptosis, "down and out" eye.

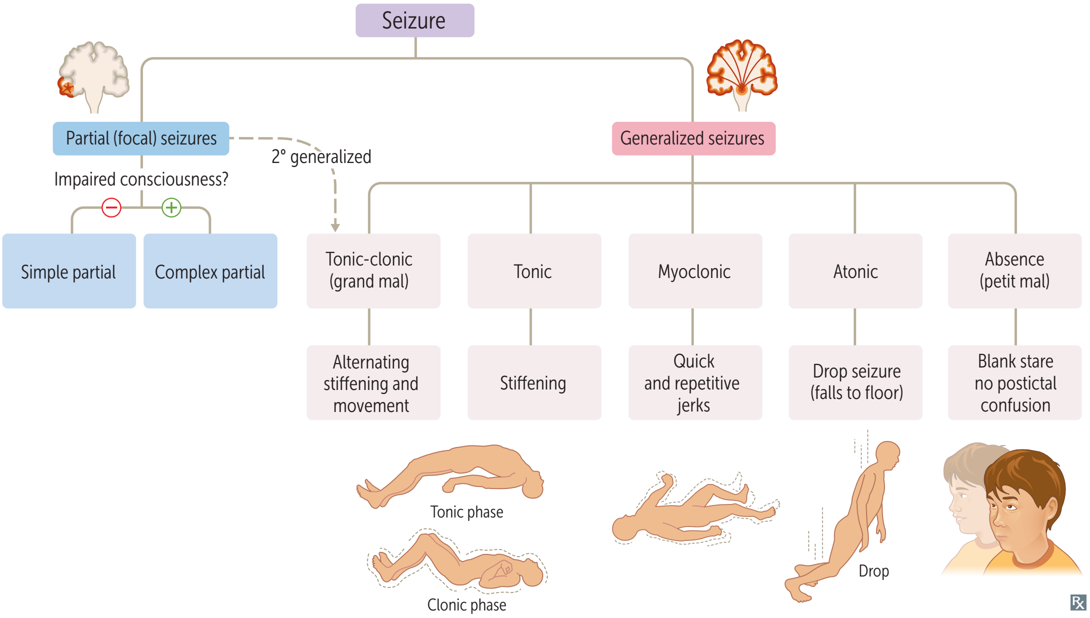
### Charcot-Bouchard microaneurysm

Common, associated with chronic hypertension; affects small vessels (eg, lenticulostriate arteries in basal ganglia, thalamus) and can cause hemorrhagic intraparenchymal strokes. Not visible on angiography.

## Fever vs heat stroke

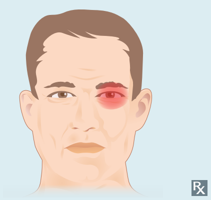
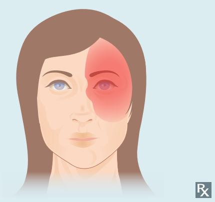
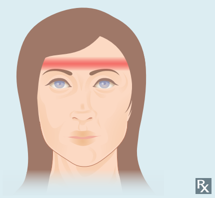
| | Fever | Heat stroke |
|---|---|---|
| PATHOPHYSIOLOGY | Cytokine activation during inflammation (eg, infection) | Inability of body to dissipate heat (eg, exertion) |
| TEMPERATURE | Usually < 40°C (104°F) | Usually > 40°C (104°F) |
| COMPLICATIONS | Febrile seizure (benign, usually self-limiting) | CNS dysfunction (eg, confusion), end-organ damage, acute respiratory distress syndrome, rhabdomyolysis |
| MANAGEMENT | Acetaminophen or ibuprofen for comfort (does not prevent future febrile seizures), antibiotic therapy if indicated | Rapid external cooling, rehydration and electrolyte correction |

| | | |
|---|---|---|
| **Seizures** | Characterized by synchronized, high-frequency neuronal firing. Variety of forms. | |
| **Partial (focal) seizures** | Affect single area of the brain. Most commonly originate in medial temporal lobe. Types:<br>▪ Simple partial (consciousness intact)—motor, sensory, autonomic, psychic<br>▪ Complex partial (impaired consciousness, automatisms) | Epilepsy—disorder of recurrent, unprovoked seizures (febrile seizures are not epilepsy).<br>Status epilepticus—continuous (≥ 5 min) or recurring seizures that may result in brain injury.<br>Causes of seizures by age:<br>▪ Children—genetic, infection (febrile), trauma, congenital, metabolic<br>▪ Adults—tumor, trauma, stroke, infection<br>▪ Elderly—stroke, tumor, trauma, metabolic, infection |
| **Generalized seizures** | Diffuse. Types:<br>▪ Absence (petit mal)—3 Hz spike-and-wave discharges, short (usually 10 seconds) and frequent episodes of blank stare, no postictal confusion. Can be triggered by hyperventilation<br>▪ Myoclonic—quick, repetitive jerks<br>▪ Tonic-clonic (grand mal)—alternating stiffening and movement, postictal confusion, urinary incontinence, tongue biting<br>▪ Tonic—stiffening<br>▪ Atonic—“drop” seizures (falls to floor); commonly mistaken for fainting | |



## Headaches

Pain due to irritation of structures such as the dura, cranial nerves, or extracranial structures. Primary headaches include cluster, migraine, and tension; migraine and tension headaches are more common in females. Secondary headaches include subarachnoid hemorrhage, meningitis, hydrocephalus, neoplasia, giant cell (temporal) arteritis.

| CLASSIFICATION | LOCALIZATION | DURATION | DESCRIPTION | TREATMENT |
|---|---|---|---|---|
| **Cluster**[a]  | Unilateral | 15 min–3 hr; repetitive | Excruciating periorbital pain ("suicide headache") with autonomic symptoms (eg, lacrimation, rhinorrhea, conjunctival injection). May present with Horner syndrome. More common in males. | Acute: sumatriptan, 100% $O_2$. Prophylaxis: verapamil. |
| **Migraine**  | Unilateral | 4–72 hr | Pulsating pain with nausea, photophobia, and/or phonophobia. May have "aura." Due to irritation of CN V, meninges, or blood vessels (release of vasoactive neuropeptides [eg, substance P, calcitonin gene-related peptide]). | Acute: NSAIDs, triptans, dihydroergotamine, antiemetics (eg, prochlorperazine, metoclopramide). Prophylaxis: lifestyle changes (eg, sleep, exercise, diet), β-blockers, amitriptyline, topiramate, valproate, botulinum toxin, anti-CGRP monoclonal antibodies. POUND–Pulsatile, One-day duration, Unilateral, Nausea, Disabling. |
| **Tension**  | Bilateral | > 30 min (typically 4–6 hr); constant | Steady, "band-like" pain. No photophobia or phonophobia. No aura. | Acute: analgesics, NSAIDs, acetaminophen. Prophylaxis: TCAs (eg, amitriptyline), behavioral therapy. |

[a]Compare with **trigeminal neuralgia**, which produces repetitive, unilateral, shooting/shock-like pain in the distribution of CN V. Triggered by chewing, talking, touching certain parts of the face. Lasts (typically) for seconds to minutes, but episodes often increase in intensity and frequency over time. First-line therapy: carbamazepine.

### Movement disorders

| DISORDER | PRESENTATION | CHARACTERISTIC LESION | NOTES |
|---|---|---|---|
| **Akathisia** | Restlessness and intense urge to move | | Can be seen with neuroleptic use or as a side effect of Parkinson treatment |
| **Asterixis** | Extension of wrists causes “flapping” motion | | Associated with hepatic encephalopathy, Wilson disease, and other metabolic derangements |
| **Athetosis** | Slow, snake-like, writhing movements; especially seen in the fingers | Basal ganglia | Seen in Huntington disease |
| **Chorea** | Sudden, jerky, purposeless movements | Basal ganglia | *Chorea* = dancing<br>Seen in Huntington disease and in acute rheumatic fever (Sydenham chorea) |
| **Dystonia** | Sustained, involuntary muscle contractions | | Writer’s cramp, blepharospasm, torticollis<br>Treatment: botulinum toxin injection |
| **Essential tremor** | High-frequency tremor with sustained posture (eg, outstretched arms), worsened with movement or when anxious | | Often familial<br>Patients often self-medicate with alcohol, which ↓ tremor amplitude<br>Treatment: nonselective β-blockers (eg, propranolol), barbiturates (primidone) |
| **Intention tremor** | Slow, zigzag motion when pointing/extending toward a target | Cerebellar dysfunction | |
| **Resting tremor** | Uncontrolled movement of distal appendages (most noticeable in hands); tremor alleviated by intentional movement | Substantia nigra (**Park**inson disease) | Occurs at rest; “pill-rolling tremor” of Parkinson disease<br>When you **park** your car, it is at **rest** |
| **Hemiballismus** | Sudden, wild flailing of one side of the body | Contralateral subthalamic nucleus (eg, lacunar stroke) | Pronounce “**Half**-of-body is going **ballis**tic” |
| **Myoclonus** | Sudden, brief, uncontrolled muscle contraction | | Jerks; hiccups; common in metabolic abnormalities (eg, renal and liver failure), Creutzfeldt-Jakob disease |
| **Restless legs syndrome** | Uncomfortable sensations in legs causing irresistible urge to move them; relieved by movement; worse at rest/nightime | | Associated with iron deficiency, CKD<br>Treatment: dopamine agonists (pramipexole, ropinirole) |

## Neurodegenerative disorders

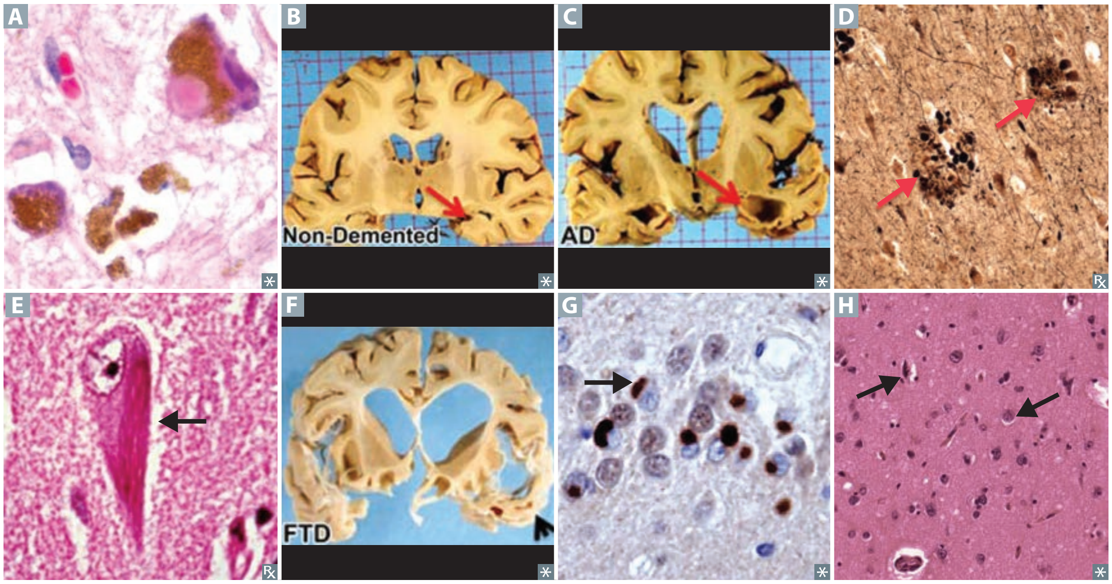
↓ in cognitive ability, memory, or function with intact consciousness.

Must rule out depression as cause of dementia (called pseudodementia). Other reversible causes of dementia: hypothyroidism, vitamin $B_{12}$ deficiency, neurosyphilis, normal pressure hydrocephalus.

| DISEASE | DESCRIPTION | HISTOLOGIC/GROSS FINDINGS |
|---|---|---|
| **Parkinson disease** | Parkinson **TRAPSS** your body:<br>**T**remor (pill-rolling tremor at rest)<br>**R**igidity (cogwheel)<br>**A**kinesia (or bradykinesia)<br>**P**ostural instability<br>**S**huffling gait<br>**S**mall handwriting (micrographia)<br>Dementia is usually a late finding.<br>MPTP, a contaminant in illegal drugs, is metabolized to MPP+, which is toxic to substantia nigra. | Loss of dopaminergic neurons (ie, depigmentation) of substantia nigra pars compacta.<br>Lewy bodies: composed of α-synuclein (intracellular eosinophilic inclusions A). |
| **Huntington disease** | Autosomal dominant trinucleotide $(CAG)_n$ repeat expansion in the **hunt**ingtin *(HTT)* gene on chromosome **4** **(4 letters).** Symptoms manifest between ages 20 and 50: chorea, athetosis, aggression, depression, dementia (sometimes initially mistaken for substance use).<br>Anticipation results from expansion of **CAG** repeats. **C**audate loses **A**Ch and **G**ABA. | Atrophy of caudate and putamen with ex vacuo ventriculomegaly.<br>↑ dopamine, ↓ GABA, ↓ ACh in brain. Neuronal death via NMDA-R binding and glutamate excitotoxicity. |
| **Alzheimer disease** | Most common cause of dementia in elderly. Down syndrome patients have ↑ risk of developing early-onset Alzheimer disease, as APP is located on chromosome 21.<br>↓ ACh.<br>Associated with the following altered proteins:<br>▪ ApoE-2: ↓ risk of sporadic form<br>▪ ApoE-4: ↑ risk of sporadic form<br>▪ APP, presenilin-1, presenilin-2: familial forms (10%) with earlier onset | Widespread cortical atrophy (normal cortex B; cortex in Alzheimer disease C), especially hippocampus (arrows in B and C). Narrowing of gyri and widening of sulci.<br>Senile plaques D in gray matter: extracellular β-amyloid core; may cause amyloid angiopathy → intracranial hemorrhage; Aβ (amyloid-β) synthesized by cleaving amyloid precursor protein (APP).<br>Neurofibrillary tangles E: intracellular, hyperphosphorylated tau protein = insoluble cytoskeletal elements; number of tangles correlates with degree of dementia.<br>Hirano bodies—intracellular eosinophilic proteinaceous rods in hippocampus. |
| **Frontotemporal dementia** | Formerly called Pick disease. Early changes in personality and behavior (behavioral variant), or aphasia (primary progressive aphasia).<br>May have associated movement disorders. | Frontotemporal lobe degeneration F.<br>Inclusions of hyperphosphorylated tau (round Pick bodies G) or ubiquitinated TDP-43. |

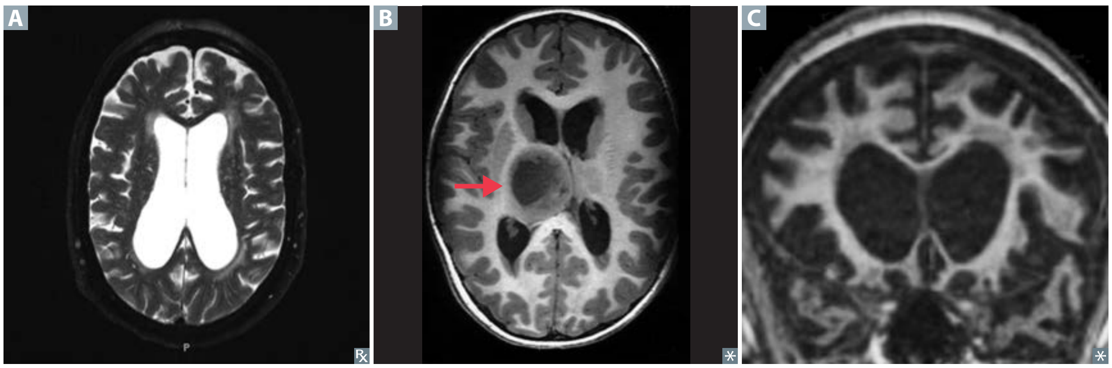
### Neurodegenerative disorders *(continued)*

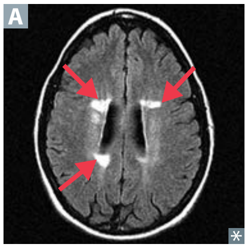
| DISEASE | DESCRIPTION | HISTOLOGIC/GROSS FINDINGS |
|---|---|---|
| **Lewy body dementia** | Visual hallucinations ("haLewycinations"), dementia with fluctuating cognition/alertness, REM sleep behavior disorder, and parkinsonism. Called Lewy body dementia if cognitive and motor symptom onset < 1 year apart, otherwise considered dementia 2° to Parkinson disease. | Intracellular Lewy bodies A primarily in cortex. |
| **Vascular dementia** | Result of multiple arterial infarcts and/or chronic ischemia.<br>Step-wise decline in cognitive ability with late-onset memory impairment. 2nd most common cause of dementia in elderly. | MRI or CT shows multiple cortical and/or subcortical infarcts. |
| **Creutzfeldt-Jakob disease** | Rapidly progressive (weeks to months) dementia with myoclonus ("startle myoclonus") and ataxia. Associated with periodic sharp waves on EEG and ↑ 14-3-3 protein in CSF. May be transmitted by contaminated materials (eg, corneal transplant, neurosurgical equipment). Fatal. | Spongiform cortex (vacuolation without inflammation).<br>Prions ($PrP^{c} \rightarrow PrP^{sc}$ sheet [β-pleated sheet resistant to proteases]) H. |
| **HIV-associated dementia** | Subcortical dysfunction associated with advanced HIV infection. Characterized by cognitive deficits, gait disturbance, irritability, depressed mood. | Diffuse gray matter and subcortical atrophy.<br>Microglial nodules with multinucleated giant cells. |



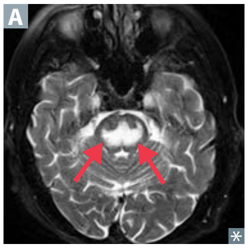
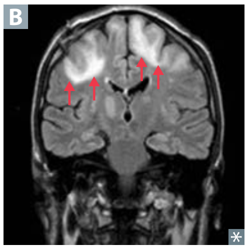
| | |
|---|---|
| **Idiopathic intracranial hypertension** | Also called pseudotumor cerebri. ↑ ICP with no obvious findings on imaging. Risk factors include **female** sex, **T**etracyclines, **O**besity, vitamin **A** excess, **D**anazol (**female TOAD**). Associated with cerebral venous sinus stenosis. Findings: headache, tinnitus, diplopia (usually from CN VI palsy), no change in mental status. Impaired optic nerve axoplasmic flow → papilledema. Visual field testing shows enlarged blind spot and peripheral constriction. Lumbar puncture reveals ↑ opening pressure and provides temporary headache relief.<br>Treatment: weight loss, acetazolamide, invasive procedures for refractory cases (eg, CSF shunt placement, optic nerve sheath fenestration surgery for visual loss). |

| | |
|---|---|
| **Hydrocephalus** | ↑ CSF volume → ventricular dilation +/– ↑ ICP. |
| **Communicating** | |
| **Communicating hydrocephalus** | ↓ CSF absorption by arachnoid granulations (eg, arachnoid scarring post-meningitis) → ↑ ICP, papilledema, herniation. |
| **Normal pressure hydrocephalus** | Affects the elderly; idiopathic; CSF pressure elevated only episodically; does not result in increased subarachnoid space volume. Expansion of ventricles A distorts the fibers of the corona radiata → triad of **urinary incontinence**, **gait apraxia** (magnetic gait), and **cognitive dysfunction**. "**Wet**, **wobbly**, and **wacky**." Symptoms potentially reversible with CSF drainage via lumbar puncture or shunt placement. |
| **Noncommunicating (obstructive)** | |
| **Noncommunicating hydrocephalus** | Caused by structural blockage of CSF circulation within ventricular system (eg, stenosis of aqueduct of Sylvius, colloid cyst blocking foramen of Monro, tumor B). |
| **Hydrocephalus mimics** | |
| **Ex vacuo ventriculomegaly** | Appearance of ↑ CSF on imaging C, but is actually due to ↓ brain tissue and neuronal atrophy (eg, Alzheimer disease, advanced HIV, frontotemporal dementia, Huntington disease). ICP is normal; NPH triad is not seen. |



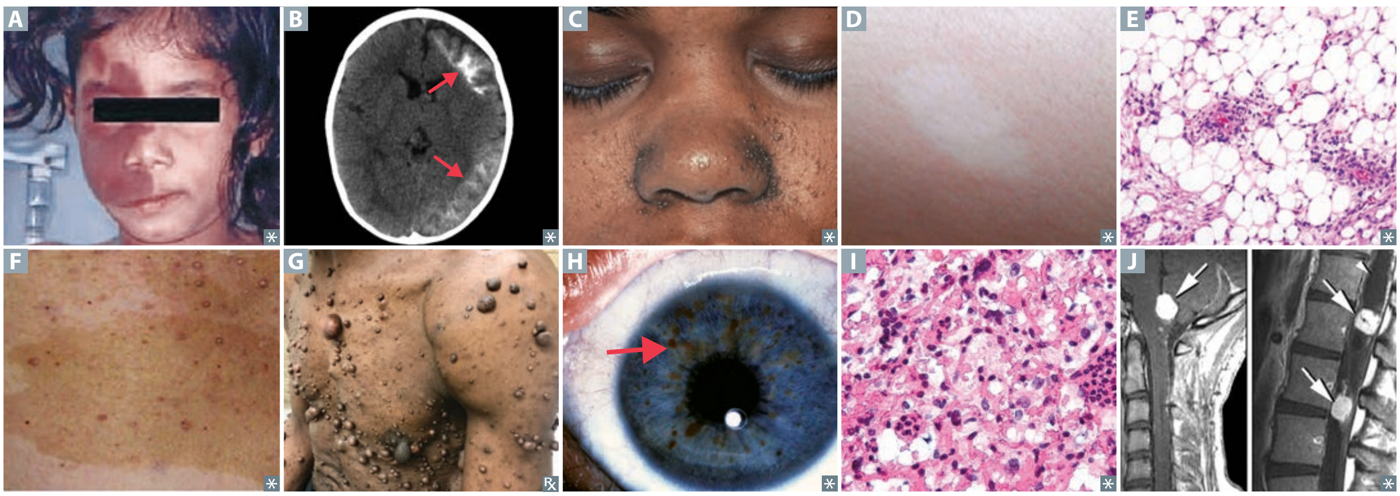
| | |
|---|---|
| **Multiple sclerosis** | Autoimmune inflammation and demyelination of CNS (brain and spinal cord) with subsequent axonal damage. Can present with:<br>▪ Acute optic neuritis (painful unilateral visual loss associated with Marcus Gunn pupil)<br>▪ Brain stem/cerebellar syndromes (eg, diplopia, ataxia, scanning speech, intention tremor, nystagmus/INO [bilateral > unilateral])<br>▪ Pyramidal tract demyelination (eg, weakness, spasticity)<br>▪ Spinal cord syndromes (eg, electric shock-like sensation along cervical spine on neck flexion, neurogenic bladder, paraparesis, sensory manifestations affecting the trunk or one or more extremity)<br>Symptoms may exacerbate with increased body temperature (eg, hot bath, exercise). Relapsing and remitting is most common clinical course. Most often affects females in their 20s and 30s; more common in individuals who grew up farther from equator and with low serum vitamin D levels. |
| FINDINGS<br> | ↑ IgG level and myelin basic protein in CSF. Oligoclonal bands are diagnostic. MRI is gold standard. Periventricular plaques A (areas of oligodendrocyte loss and reactive gliosis). Multiple white matter lesions disseminated in space and time. |
| TREATMENT | Stop relapses and halt/slow progression with disease-modifying therapies (eg, β-interferon, glatiramer, natalizumab). Treat acute flares with IV steroids. Symptomatic treatment for neurogenic bladder (catheterization, muscarinic antagonists), spasticity (baclofen, $GABA_B$ receptor agonists), pain (TCAs, anticonvulsants). |

## Other demyelinating and dysmyelinating disorders

| | |
|---|---|
| **Osmotic demyelination syndrome**  | Also called central pontine myelinolysis. Massive axonal demyelination in pontine white matter A 2° to rapid osmotic changes, most commonly iatrogenic correction of hyponatremia but also rapid shifts of other osmolytes (eg, glucose). Acute paralysis, dysarthria, dysphagia, diplopia, loss of consciousness. Can cause "locked-in syndrome."<br>Correcting serum $Na^+$ too fast:<br>▪ "From low to high, your pons will die" (osmotic demyelination syndrome)<br>▪ "From high to low, your brains will blow" (cerebral edema/herniation) |
| **Acute inflammatory demyelinating polyneuropathy** | Most common subtype of **Guillain-Barré syndrome**.<br>Autoimmune condition that destroys Schwann cells via inflammation and demyelination of motor fibers, sensory fibers, peripheral nerves (including CN III-XII). Likely facilitated by molecular mimicry and triggered by inoculations or stress. Despite association with infections (eg, *Campylobacter jejuni*, viruses [eg, Zika]), no definitive causal link to any pathogen.<br>Results in symmetric ascending muscle weakness/paralysis and depressed/absent DTRs beginning in lower extremities. Facial paralysis (usually bilateral) and respiratory failure are common. May see autonomic dysregulation (eg, cardiac irregularities, hypertension, hypotension) or sensory abnormalities. Most patients survive with good functional recovery.<br>↑ CSF protein with normal cell count (albuminocytologic dissociation).<br>Respiratory support is critical until recovery. Disease-modifying treatment: plasma exchange or IV immunoglobulins. No role for steroids. |
| **Acute disseminated (postinfectious) encephalomyelitis** | Multifocal inflammation and demyelination after infection or vaccination. Presents with rapidly progressive multifocal neurologic symptoms, altered mental status. |
| **Charcot-Marie-Tooth disease** | Also called hereditary motor and sensory neuropathy. Group of progressive hereditary nerve disorders related to the defective production of proteins involved in the structure and function of peripheral nerves or the myelin sheath. Typically autosomal dominant and associated with foot deformities (eg, pes cavus, hammer toe), lower extremity weakness (eg, foot drop), and sensory deficits (Can't Move Toes). Most common type, CMT1A, is caused by *PMP22* gene duplication. |
| **Progressive multifocal leukoencephalopathy**  | Demyelination of CNS B due to destruction of oligodendrocytes (2° to reactivation of latent JC virus infection). Associated with severe immunosuppression (eg, lymphomas and leukemias, AIDS, organ transplantation). Rapidly progressive, usually fatal. Predominantly involves parietal and occipital areas; visual symptoms are common. ↑ risk associated with natalizumab and rituximab. |
| **Other disorders** | Krabbe disease, metachromatic leukodystrophy, adrenoleukodystrophy. |

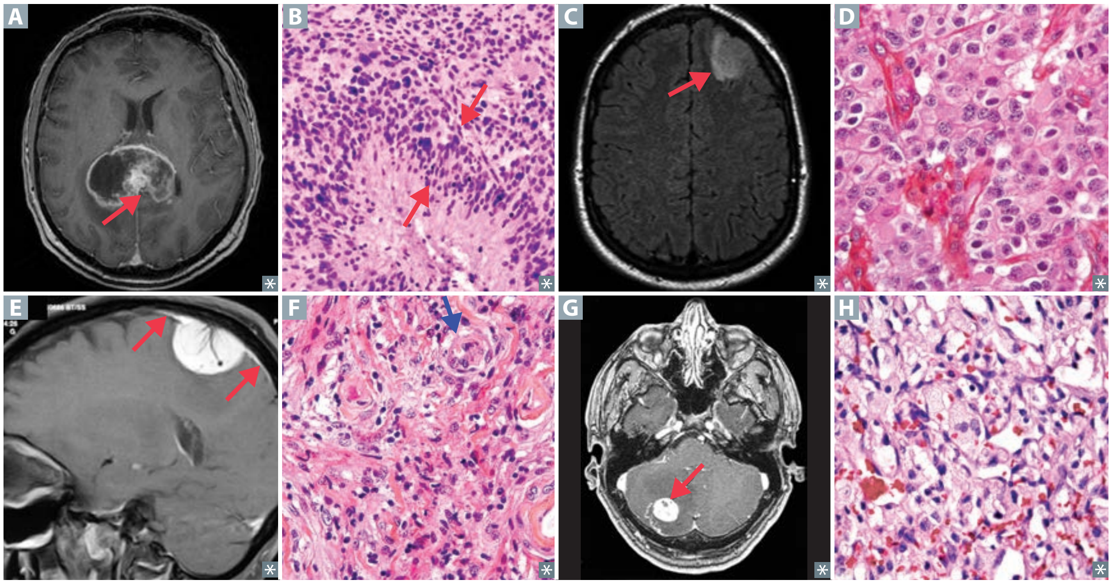
### Neurocutaneous disorders

| DISORDER | GENETICS | PRESENTATION | NOTES |
|---|---|---|---|
| **Sturge-Weber syndrome** | Congenital nonhereditary anomaly of neural crest derivatives. Somatic mosaicism of an activating mutation in one copy of the *GNAQ* gene. | Capillary vascular malformation → port-wine stain A (nevus flammeus or non-neoplastic birthmark) in CN $V_1/V_2$ distribution; ipsilateral leptomeningeal angioma with calcifications B → seizures/epilepsy; intellectual disability; episcleral hemangioma → ↑ IOP → early-onset glaucoma. | Also called encephalotrigeminal angiomatosis. |
| **Tuberous sclerosis** | AD, variable expression. Mutation in tumor suppressor genes *TSC1* on chromosome 9 (hamartin), *TSC2* on chromosome 16 (tuberin; pronounce "**two**berin"). | Hamartomas in CNS and skin, angiofibromas C, mitral regurgitation, ash-leaf spots D, cardiac rhabdomyoma, intellectual disability, renal angiomyolipoma E, seizures, shagreen patches. | Autosomal dominant. ↑ incidence of subependymal giant cell astrocytomas and ungual fibromas. |
| **Neurofibromatosis type I** | AD, 100% penetrance. Mutation in *NF1* tumor suppressor gene on chromosome 17 (encodes neurofibromin, a negative RAS regulator). | **C**afé-au-lait spots F, **I**ntellectual disability, **C**utaneous neurofibromas G, **L**isch nodules (pigmented iris hamartomas H), **O**ptic gliomas, **P**heochromocytomas, **S**eizures/focal neurologic **S**igns (often from meningioma), bone lesions (eg, sphenoid dysplasia). | Also called von Recklinghausen disease. 17 letters in "von Recklinghausen." CICLOPSS. |
| **Neurofibromatosis type II** | AD. Mutation in *NF2* tumor suppressor gene (merlin) on chromosome 22. | Bilateral vestibular schwannomas, juvenile cataracts, meningiomas, ependymomas. | NF2 affects 2 ears, 2 eyes. |
| **von Hippel-Lindau disease** | AD. Deletion of *VHL* gene on chromosome 3p. pVHL ubiquitinates hypoxia-inducible factor 1a. | **H**emangioblastomas (high vascularity with hyperchromatic nuclei I) in retina, brain stem, cerebellum, spine J; **A**ngiomatosis; bilateral **R**enal cell carcinomas; **P**heochromocytomas. | Numerous tumors, benign and malignant. HARP. VHL = 3 letters = chromosome 3; associated with RCC (also 3 letters). |



## Adult primary brain tumors

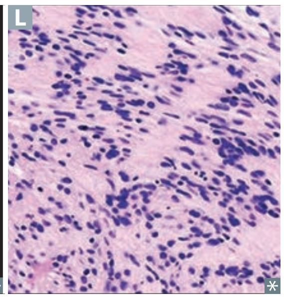
| TUMOR | DESCRIPTION | HISTOLOGY |
| --- | --- | --- |
| **Glioblastoma** | Grade IV astrocytoma. Common, highly malignant 1° brain tumor with ~ 1-year median survival. Found in cerebral hemispheres. Can cross corpus callosum ("butterfly glioma" A). Associated with *EGFR* amplification. | Astrocyte origin, GFAP ⊕. "Pseudopalisading" pleomorphic tumor cells B border central areas of necrosis, hemorrhage, and/or microvascular proliferation. |
| **Oligodendroglioma** | Relatively rare, slow growing. Most often in frontal lobes C.<br>Often calcified. | Oligodendrocyte origin. "Fried egg" cells—round nuclei with clear cytoplasm D.<br>"Chicken-wire" capillary pattern. |
| **Meningioma** | Common, typically benign. Females > males. Most often occurs near surfaces of brain and in parasagittal region. Extra-axial (external to brain parenchyma) and may have a dural attachment ("tail" E). Often asymptomatic; may present with seizures or focal neurologic signs. Resection and/or radiosurgery. | Arachnoid cell origin. Spindle cells concentrically arranged in a whorled pattern F; psammoma bodies (laminated calcifications). |
| **Hemangioblastoma** | Most often cerebellar G. Associated with von Hippel-Lindau syndrome when found with retinal angiomas. Can produce erythropoietin → 2° polycythemia. | Blood vessel origin. Closely arranged, thin-walled capillaries with minimal intervening parenchyma H. |



### Adult primary brain tumors *(continued)*

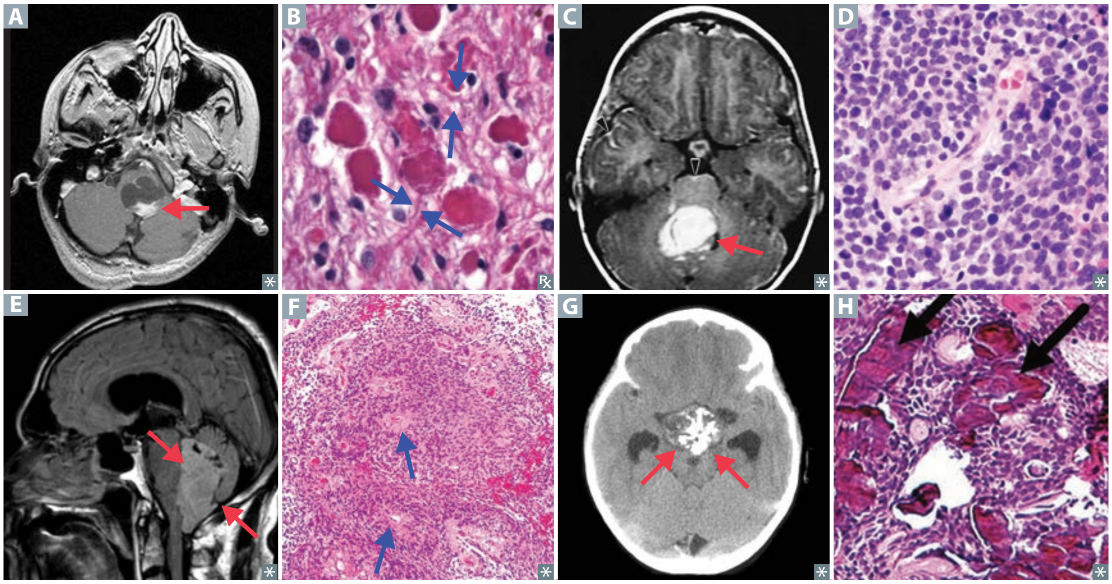
| TUMOR | DESCRIPTION | HISTOLOGY |
|---|---|---|
| **Pituitary adenoma** | May be nonfunctioning (silent) or hyperfunctioning (hormone-producing). Nonfunctional tumors present with mass effect (eg, bitemporal hemianopia [due to pressure on optic chiasm I]). Pituitary apoplexy → hyper- or hypopituitarism.<br>Prolactinoma classically presents as galactorrhea, amenorrhea, ↓ bone density due to suppression of estrogen in females and as ↓ libido, infertility in males.<br>Treatment: dopamine agonists (eg, bromocriptine, cabergoline), transsphenoidal resection. | Hyperplasia of only one type of endocrine cells found in pituitary. Most commonly from lactotrophs (prolactin) J → hyperprolactinemia. Less commonly, from somatotrophs (GH) → acromegaly, gigantism; corticotrophs (ACTH) → Cushing disease. Rarely, from thyrotrophs (TSH), gonadotrophs (FSH, LH). |
| **Schwannoma** | Classically at the cerebellopontine angle K, benign, involving CNs V, VII, and VIII, but can be along any peripheral nerve. Often localized to CN VIII in internal acoustic meatus → vestibular schwannoma (can present as hearing loss and tinnitus). Bilateral vestibular schwannomas found in NF-2. Resection or stereotactic radiosurgery. | Schwann cell origin, S-100 ⊕. Biphasic, dense, hypercellular areas containing spindle cells alternating with hypocellular, myxoid areas L. |



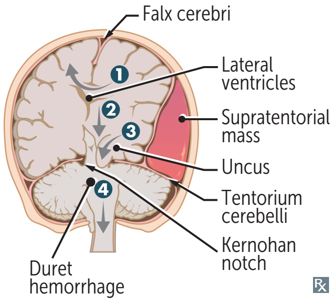



## Childhood primary brain tumors

| TUMOR | DESCRIPTION | HISTOLOGY |
|---|---|---|
| **Pilocytic astrocytoma** | Low-grade astrocytoma. Most common 1° brain tumor in childhood. Usually well circumscribed. In children, most often found in posterior fossa A (eg, cerebellum). May be supratentorial. Benign; good prognosis. | Astrocyte origin, GFAP ⊕. Bipolar neoplastic cells with hair-like projections. Associated with microcysts and Rosenthal fibers (eosinophilic, corkscrew fibers B). Cystic + solid (gross). |
| **Medulloblastoma** | Most common malignant brain tumor in childhood. Commonly involves cerebellum C. Can compress 4th ventricle, causing noncommunicating hydrocephalus → headaches, papilledema. Can involve the cerebellar vermis → truncal ataxia. Can send "drop metastases" to spinal cord. | Form of primitive neuroectodermal tumor (PNET). Homer-Wright rosettes, small blue cells D.<br>Synaptophysin ⊕. |
| **Ependymoma** | Most commonly found in 4th ventricle E. Can cause hydrocephalus. Poor prognosis. | Ependymal cell origin. Characteristic perivascular pseudorosettes F. Rod-shaped blepharoplasts (basal ciliary bodies) found near the nucleus. |
| **Craniopharyngioma** | Most common childhood supratentorial tumor. May be confused with pituitary adenoma (both cause bitemporal hemianopia). Associated with a high recurrence rate. | Derived from remnants of Rathke pouch (ectoderm). Calcification is common G H. Cholesterol crystals found in "motor oil"-like fluid within tumor. |
| **Pinealoma** | Tumor of pineal gland. Can cause Parinaud syndrome (compression of tectum → vertical gaze palsy); obstructive hydrocephalus (compression of cerebral aqueduct); precocious puberty in males (hCG production). | Similar to germ cell tumors (eg, testicular seminoma). |



## Herniation syndromes

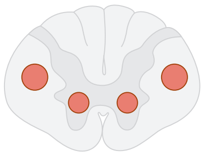
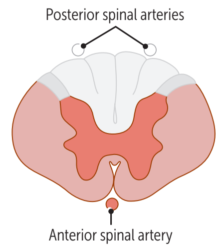
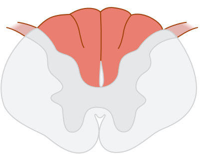
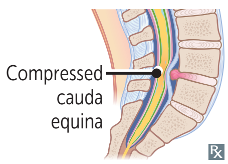



| | |
|---|---|
| ❶ Cingulate (subfalcine) herniation under falx cerebri | Can compress anterior cerebral artery. |
| ❷ Central/downward transtentorial herniation | Caudal displacement of brain stem → rupture of paramedian basilar artery branches → Duret hemorrhages. Usually fatal. |
| ❸ Uncal transtentorial herniation | Uncus = medial temporal lobe. Early herniation → ipsilateral blown pupil (unilateral CN III compression), contralateral hemiparesis. Late herniation → coma, Kernohan phenomenon (misleading contralateral blown pupil and ipsilateral hemiparesis due to contralateral compression against Kernohan notch). |
| ❹ Cerebellar tonsillar herniation into the foramen magnum | Coma and death result when these herniations compress the brain stem. |

## Motor neuron signs

| SIGN | UMN LESION | LMN LESION | COMMENTS |
|---|---|---|---|
| Weakness | + | + | **Lower** motor neuron (LMN) = everything **lowered** (less muscle mass, ↓ muscle tone, ↓ reflexes, downgoing toes) |
| Atrophy | – | + | **Up**per motor neuron (UMN) = everything **up** (tone, DTRs, toes) |
| Fasciculations | – | + | Fasciculations = muscle twitching |
| Reflexes | ↑ | ↓ | Positive Babinski is normal in infants |
| Tone | ↑ | ↓ | |
| Babinski | + | – | |
| Spastic paresis | + | – | |
| Flaccid paralysis | – | + | |
| Clasp knife spasticity | + | – | |

## Spinal lesions

| AREA AFFECTED | DISEASE | CHARACTERISTICS |
| --- | --- | --- |
|  | **Spinal muscular atrophy** | Congenital degeneration of anterior horns. LMN symptoms only, symmetric weakness. "Floppy baby" with marked hypotonia (flaccid paralysis) and tongue fasciculations. Autosomal recessive *SMN1* mutation → defective snRNP assembly. SMA type 1 is called Werdnig-Hoffmann disease. |
|  | **Amyotrophic lateral sclerosis** | Also called Lou Gehrig disease. Combined UMN (corticobulbar/corticospinal) and LMN (medullary and spinal cord) degeneration. No sensory or bowel/bladder deficits.<br>Can be caused by defect in superoxide dismutase 1.<br>LMN deficits: flaccid limb weakness, fasciculations, atrophy, bulbar palsy (dysarthria, dysphagia, tongue atrophy). UMN deficits: spastic limb weakness, hyperreflexia, clonus, pseudobulbar palsy (dysarthria, dysphagia, emotional lability). Fatal (most often from respiratory failure).<br>Treatment: "riLouzole". |
|   | **Complete occlusion of anterior spinal artery** | Spares dorsal columns and Lissauer tract; mid-thoracic ASA territory is watershed area, as artery of Adamkiewicz supplies ASA below T8. Can be caused by aortic aneurysm repair. Presents with UMN deficit below the lesion (corticospinal tract), LMN deficit at the level of the lesion (anterior horn), and loss of pain and temperature sensation below the lesion (spinothalamic tract). |
|  | **Tabes dorsalis** | Caused by 3° syphilis. Results from degeneration/demyelination of dorsal columns and roots → progressive sensory ataxia (impaired proprioception → poor coordination). ⊕ Romberg sign and absent DTRs. Associated with Charcot joints, shooting pain, Argyll Robertson pupils. |
|  | **Syringomyelia** | Syrinx expands and damages anterior white commissure of spinothalamic tract (2nd-order neurons) → bilateral symmetric loss of pain and temperature sensation in cape-like distribution. Seen with Chiari I malformation. Can affect other tracts. |
|  | **Vitamin $B_{12}$ deficiency** | Subacute combined degeneration (SCD)—demyelination of Spinocerebellar tracts, lateral Corticospinal tracts, and Dorsal columns. Ataxic gait, paresthesia, impaired position/vibration sense (⊕ Romberg sign), UMN symptoms. |
|   | **Cauda equina syndrome** | Compression of spinal roots L2 and below, often due to intervertebral disc herniation or tumor.<br>Radicular pain, absent knee and ankle reflexes, loss of bladder and anal sphincter control, saddle anesthesia. |

## Poliomyelitis

Caused by poliovirus (fecal-oral transmission). Replicates in lymphoid tissue of oropharynx and small intestine before spreading via bloodstream to CNS. Infection causes destruction of cells in anterior horn of spinal cord (LMN death).

Signs of LMN lesion: asymmetric weakness (vs symmetric weakness in spinal muscular atrophy), hypotonia, flaccid paralysis, fasciculations, hyporeflexia, muscle atrophy. Respiratory muscle involvement leads to respiratory failure. Signs of infection: malaise, headache, fever, nausea, etc.

CSF shows ↑ WBCs (lymphocytic pleocytosis) and slight ↑ of protein (with no change in CSF glucose). Virus recovered from stool or throat.

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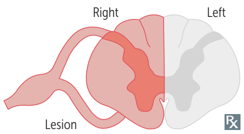
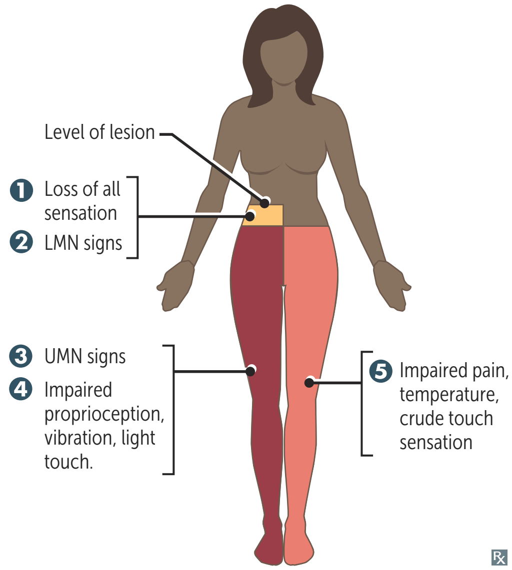
## Brown-Séquard syndrome




Hemisection of spinal cord. Findings:

1. Ipsilateral loss of all sensation **at** level of lesion
2. Ipsilateral LMN signs (eg, flaccid paralysis) **at** level of lesion
3. Ipsilateral UMN signs **below** level of lesion (due to corticospinal tract damage)
4. Ipsilateral loss of proprioception, vibration, and light (2-point discrimination) touch **below** level of lesion (due to dorsal column damage)
5. Contralateral loss of pain, temperature, and crude (non-discriminative) touch **below** level of lesion (due to spinothalamic tract damage)

If lesion occurs above T1, patient may present with ipsilateral Horner syndrome due to damage of oculosympathetic pathway.

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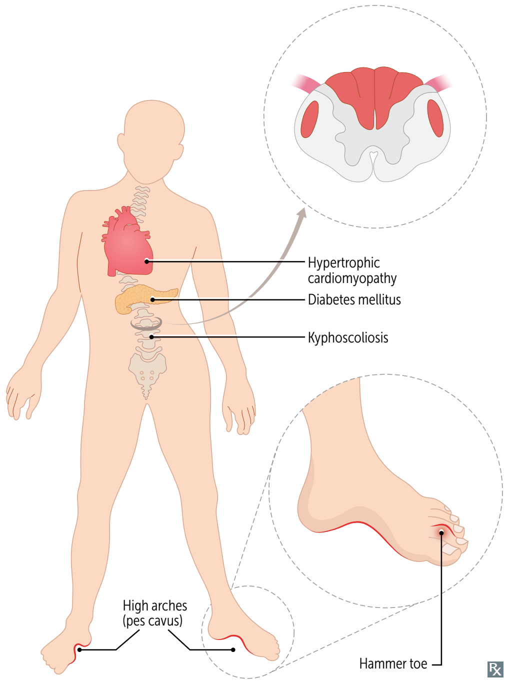
## Friedreich ataxia


Autosomal recessive trinucleotide repeat disorder $(GAA)_n$ on chromosome 9 in gene that encodes frataxin (iron-binding protein). Leads to impairment in mitochondrial functioning. Degeneration of lateral corticospinal tract (spastic paralysis), spinocerebellar tract (ataxia), dorsal columns (↓ vibratory sense, proprioception), and dorsal root ganglia (loss of DTRs). Staggering gait, frequent falling, nystagmus, dysarthria, pes cavus, hammer toes, diabetes mellitus, hypertrophic cardiomyopathy (cause of death). Presents in childhood with kyphoscoliosis A.

Friedreich is fratastic (frataxin): he's your favorite frat brother, always staggering and falling but has a sweet, big heart. Ataxic GAAit.



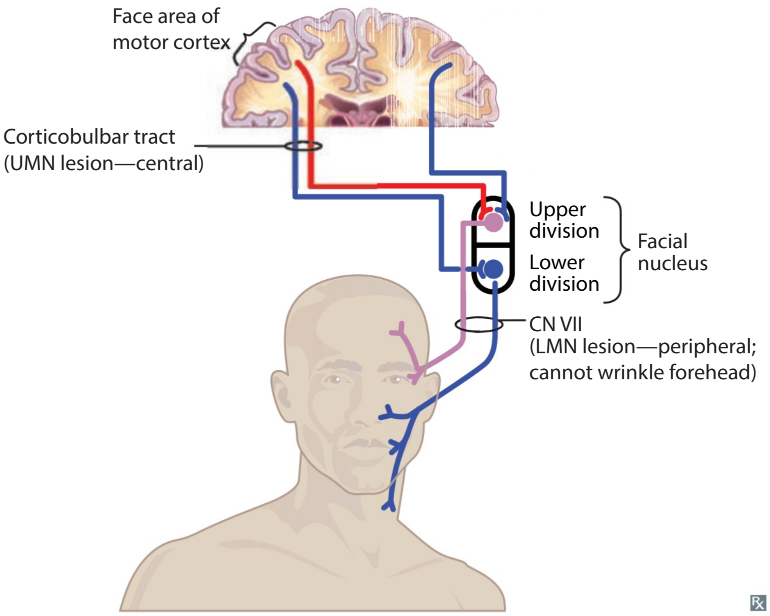
## Common cranial nerve lesions

| | |
|---|---|
| **CN V motor lesion** | Jaw deviates **toward** side of lesion due to unopposed force from the opposite pterygoid muscle. |
| **CN X lesion** | Uvula deviates **away** from side of lesion. Weak side collapses and uvula points away. |
| **CN XI lesion** | Weakness turning head to contralateral side of lesion (SCM). Shoulder droop on side of lesion (trapezius).<br>The left SCM contracts to help turn the head to the right. |
| **CN XII lesion** | LMN lesion. Tongue deviates **toward** side of lesion ("lick your wounds") due to weakened tongue muscles on affected side. |

## Facial nerve lesions

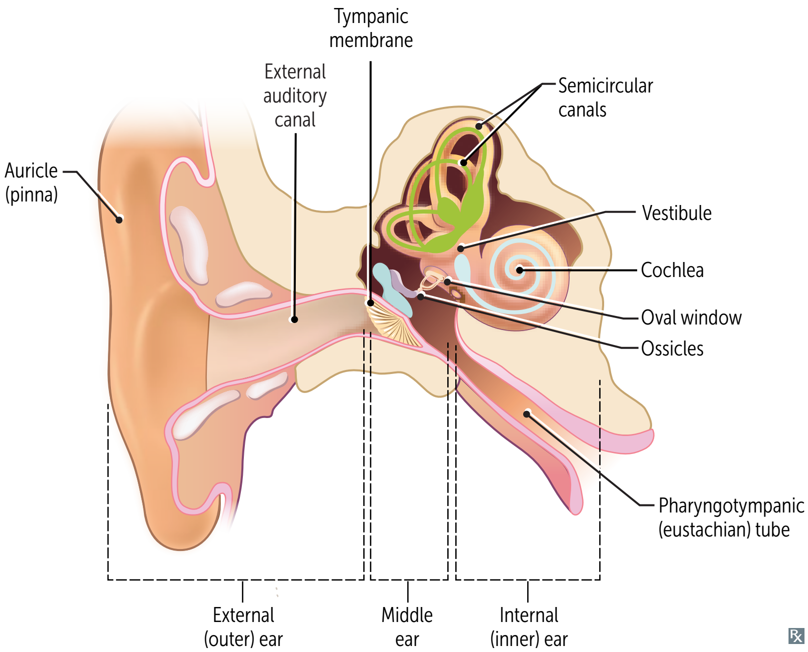

**Bell palsy** is the most common cause of peripheral facial palsy A. Usually develops after HSV reactivation. Treatment: corticosteroids +/– acyclovir. Most patients gradually recover function, but aberrant regeneration can occur. Other causes of peripheral facial palsy include Lyme disease, herpes zoster (Ramsay Hunt syndrome), sarcoidosis, tumors (eg, parotid gland), diabetes mellitus.

| | Upper motor neuron lesion | Lower motor neuron lesion |
|---|---|---|
| LESION LOCATION | Motor cortex, connection from motor cortex to facial nucleus in pons | Facial nucleus, anywhere along CN VII |
| AFFECTED SIDE | Contralateral | Ipsilateral |
| MUSCLES INVOLVED | Lower muscles of facial expression | Upper and lower muscles of facial expression |
| FOREHEAD INVOLVED? | Spared, due to bilateral UMN innervation | Affected |
| OTHER SYMPTOMS | Variable; depends on size of lesion | Incomplete eye closure (dry eyes, corneal ulceration), hyperacusis, loss of taste sensation to anterior tongue |



## ▶ NEUROLOGY—OTOLOGY

### Auditory anatomy and physiology

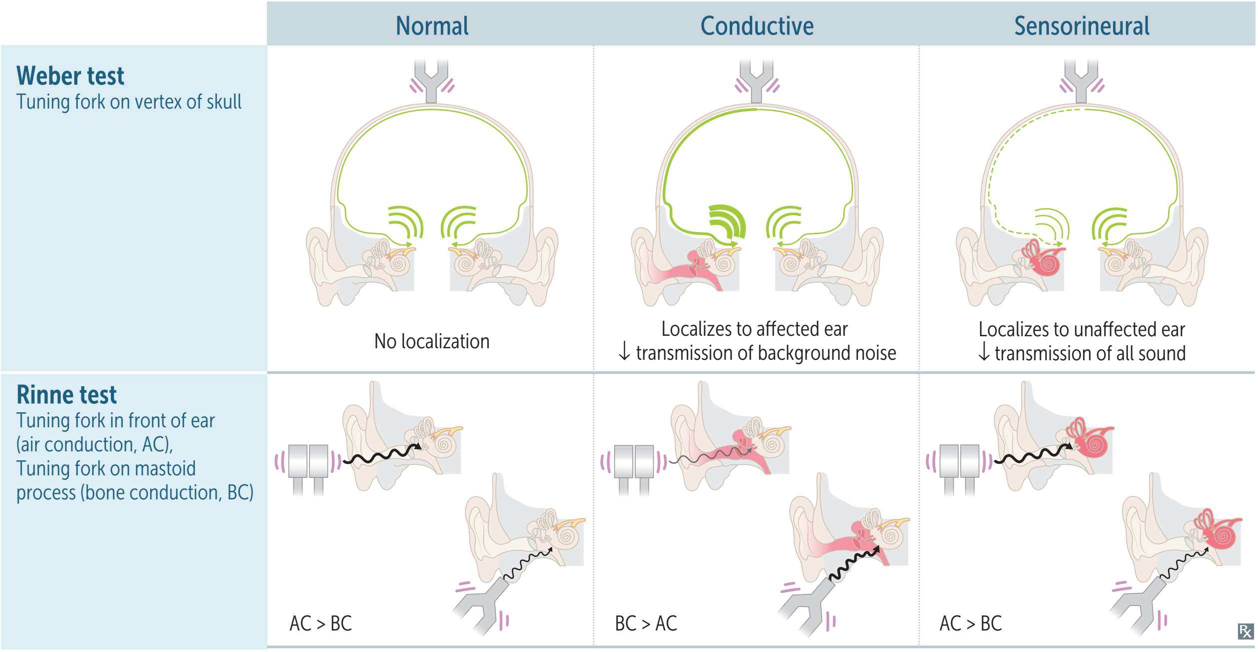



| | |
|---|---|
| **Outer ear** | Visible portion of ear (pinna), includes auditory canal and tympanic membrane. Transfers sound waves via vibration of tympanic membrane. |
| **Middle ear** | Air-filled space with three bones called the ossicles (malleus, incus, stapes). Ossicles conduct and amplify sound from tympanic membrane to inner ear. |
| **Inner ear** | Snail-shaped, fluid-filled cochlea. Contains basilar membrane that vibrates 2° to sound waves. Vibration transduced via specialized hair cells → auditory nerve signaling → brain stem.<br>Each frequency leads to vibration at specific location on basilar membrane (tonotopy):<br>▪ Low frequency heard at apex near helicotrema (wide and flexible).<br>▪ High frequency heard best at base of cochlea (thin and rigid). |

### Types of hearing loss

| | |
|---|---|
| **Noise-induced hearing loss** | Damage to stereociliated cells in organ of Corti. Loss of high-frequency hearing first. Sudden extremely loud noises can produce hearing loss due to tympanic membrane rupture. |
| **Presbycusis** | Aging-related progressive bilateral/symmetric sensorineural hearing loss (often of higher frequencies) due to destruction of hair cells at the cochlear base (preserved low-frequency hearing at apex). |

## Diagnosing hearing loss

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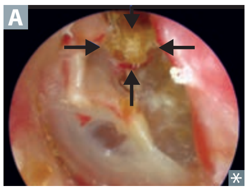
**Cholesteatoma**




Overgrowth of desquamated keratin debris within the middle ear space (A, arrows). Can be congenital or acquired (eg, 2° to recurrent/chronic otitis media). May erode ossicles, mastoid air cells → conductive hearing loss. Often presents with painless otorrhea.

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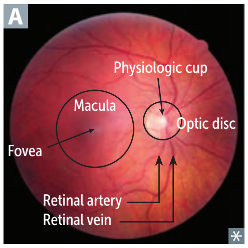
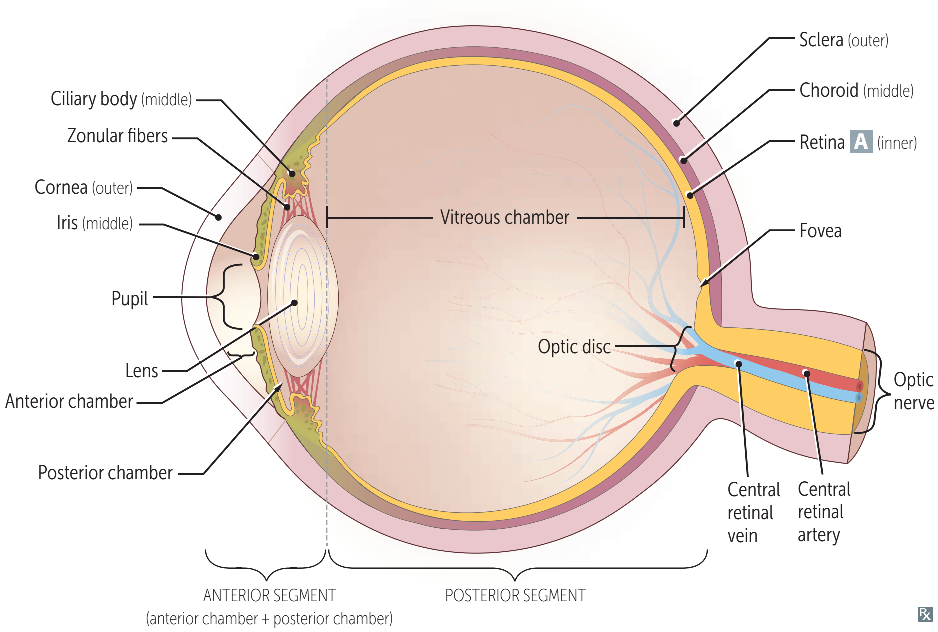
| | |
|---|---|
| **Vertigo** | Sensation of spinning while actually stationary. Subtype of "dizziness," but distinct from "lightheadedness." Peripheral vertigo more common than central vertigo. |
| **Peripheral vertigo** | Due to inner ear pathologies such as semicircular canal debris (benign paroxysmal positional vertigo, BPPV), vestibular nerve infection, Ménière disease—triad of sensorineural hearing loss, vertigo, tinnitus; endolymphatic hydrops → ↑ endolymph within the inner ear.<br>Treatment: antihistamines, anticholinergics, antiemetics (symptomatic relief); low-salt diet +/– diuretics (Ménière disease); Epley maneuver (BPPV). |
| **Central vertigo** | Brain stem or cerebellar lesion (eg, stroke affecting vestibular nuclei, demyelinating disease, or posterior fossa tumor). Findings: directional or purely vertical nystagmus, skew deviation (vertical misalignment of the eyes), diplopia, dysmetria. Focal neurologic findings. |

# ▶ NEUROLOGY—OPHTHALMOLOGY

## Normal eye anatomy

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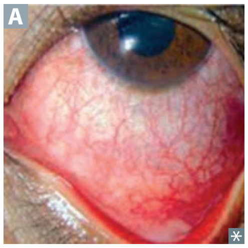
## Conjunctivitis




Inflammation of the conjunctiva → red eye A.
Allergic—itchy eyes, bilateral.
Bacterial—pus; treat with antibiotics.
Viral—most common, often adenovirus; sparse mucous discharge, swollen preauricular node, ↑ lacrimation; self-resolving.

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| | |
|---|---|
| **Refractive errors** | Common cause of impaired vision, correctable with glasses. |
| **Hyperopia** | Also called "farsightedness." Eye too short for refractive power of cornea and lens → light focused behind retina. Correct with convex (converging) lenses. |
| **Myopia** | Also called "nearsightedness." Eye too long for refractive power of cornea and lens → light focused in front of retina. Correct with concave (diverging) lens. |
| **Astigmatism** | Abnormal curvature of cornea → different refractive power at different axes. Correct with cylindrical lens. |

**Presbyopia**

Aging-related impaired accommodation (focusing on near objects), primarily due to ↓ lens elasticity, changes in lens curvature, ↓ strength of the ciliary muscle. Patients often need "reading glasses" (magnifiers).

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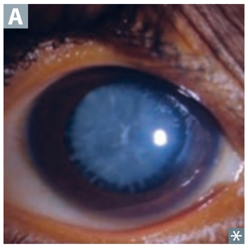
**Cataract**




Painless, often bilateral, opacification of lens A. Can result in glare and ↓ vision, especially at night, and loss of the red reflex. Acquired risk factors: ↑ age, tobacco smoking, alcohol overuse, excessive sunlight, prolonged corticosteroid use, diabetes mellitus, trauma, infection. Congenital risk factors: classic galactosemia, galactokinase deficiency, trisomies (13, 18, 21), TORCH infections (eg, rubella), Marfan syndrome, Alport syndrome, myotonic dystrophy, neurofibromatosis 2.

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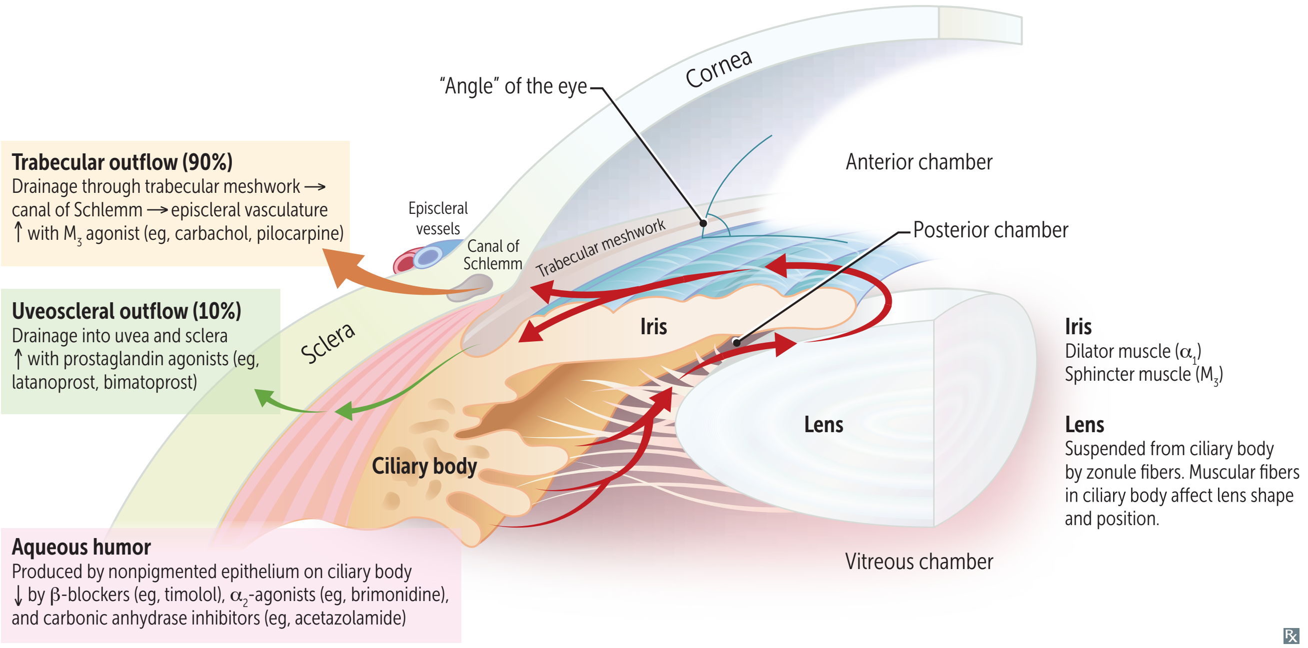
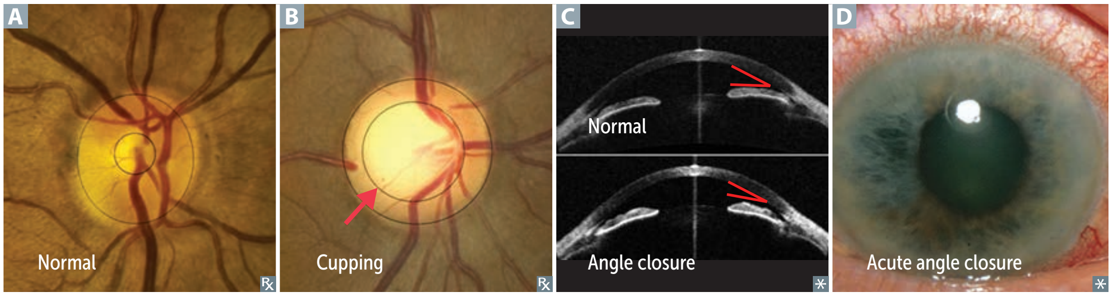
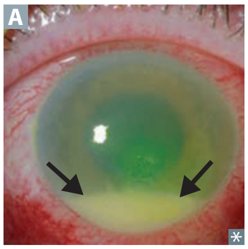
**Aqueous humor pathway**



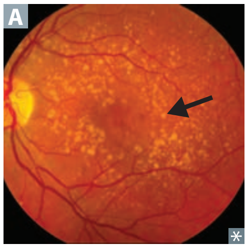
| | |
|---|---|
| **Glaucoma** | Optic disc atrophy with characteristic cupping (normal A versus thinning of outer rim of optic nerve head B), usually with elevated intraocular pressure (IOP) and progressive peripheral visual field loss if untreated. Treatment is through pharmacologic or surgical lowering of IOP. |
| **Open-angle glaucoma** | ↑ incidence in older people, Black people, and patients with family history of condition. Painless, more common in US.<br>Primary—cause unclear.<br>Secondary—blocked trabecular meshwork from WBCs (eg, uveitis), RBCs (eg, vitreous hemorrhage), retinal elements (eg, retinal detachment). |
| **Closed- or narrow-angle glaucoma** | Primary—enlargement or anterior movement of lens against central iris (pupil margin) → obstruction of normal aqueous flow through pupil → fluid builds up behind iris, pushing peripheral iris against cornea C and impeding flow through trabecular meshwork.<br>Secondary—hypoxia from retinal disease (eg, diabetes mellitus, vein occlusion) induces vasoproliferation in iris that contracts angle.<br>Chronic closure—often asymptomatic with damage to optic nerve and peripheral vision.<br>Acute closure—true ophthalmic emergency. ↑ IOP pushes iris forward → angle closes abruptly. Very painful, red eye D, sudden vision loss, halos around lights, frontal headache, fixed and mid-dilated pupil, nausea and vomiting. Mydriatic agents contraindicated. **H**urts in a **h**urry with **h**alos, a **h**eadache, and a "**h**alf-dilated" pupil. |




| | |
|---|---|
| **Uveitis** | Inflammation of uvea; specific name based on location within affected eye. Anterior uveitis: iritis; posterior uveitis: choroiditis and/or retinitis. May have hypopyon (accumulation of pus in anterior chamber A) or conjunctival redness. Associated with systemic inflammatory disorders (eg, sarcoidosis, rheumatoid arthritis, juvenile idiopathic arthritis, HLA-B27–associated conditions). |



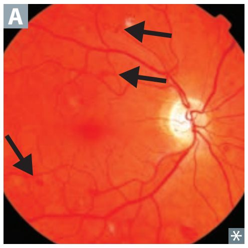
### Age-related macular degeneration




Degeneration of macula (central area of retina). Causes distortion of straight lines (metamorphopsia) and eventual loss of central vision (scotomas).

- Dry (nonexudative, > 80%)—deposition of yellowish extracellular material ("drusen") in between Bruch membrane and retinal pigment epithelium A with gradual ↓ in vision. Prevent progression with multivitamin and antioxidant supplements.
- Wet (exudative, 10–15%)—rapid loss of vision due to bleeding 2° to choroidal neovascularization. Treat with anti-VEGF (vascular endothelial growth factor) injections (eg, bevacizumab, ranibizumab).

### Diabetic retinopathy




Retinal damage due to chronic hyperglycemia. Two types:

- Nonproliferative—damaged capillaries leak blood → lipids and fluid seep into retina → hemorrhages (arrows in A) and macular edema. Treatment: blood sugar control.
- Proliferative—chronic hypoxia results in new blood vessel formation with resultant traction on retina → retinal detachment. Treatment: anti-VEGF injections, peripheral retinal photocoagulation, surgery.

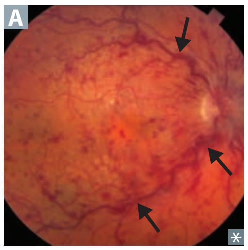
### Hypertensive retinopathy


Chronic uncontrolled hypertension → endothelial disruption → fibrinoid necrosis → retinal damage.

Flame-shaped retinal hemorrhages, arteriovenous nicking, microaneurysms, macular star (exudate, red arrow in A), cotton-wool spots (blue arrow in A). Presence of papilledema requires immediate lowering of BP.

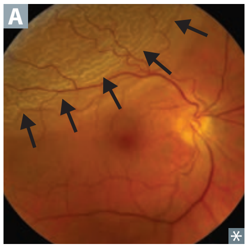
Associated with ↑ risk of stroke, CAD, kidney disease.

### Retinal vein occlusion




Blockage of central or branch retinal vein due to compression from nearby arterial atherosclerosis. Retinal hemorrhage and venous engorgement ("blood and thunder appearance"; arrows in A), edema in affected area.

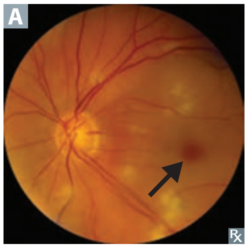
## Retinal detachment




Separation of neurosensory layer of retina (photoreceptor layer with rods and cones) from outermost pigmented epithelium (normally shields excess light, supports retina) → degeneration of photoreceptors → vision loss. May be 2° to retinal breaks, diabetic traction, inflammatory effusions. Visualized on fundoscopy as crinkling of retinal tissue A and changes in vessel direction.

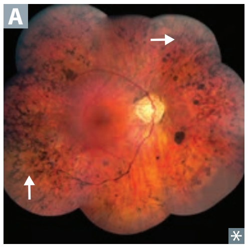
Breaks more common in patients with high myopia and/or history of head trauma. Often preceded by posterior vitreous detachment ("flashes" and "floaters") and eventual monocular loss of vision like a "curtain drawn down." Surgical emergency.

## Central retinal artery occlusion



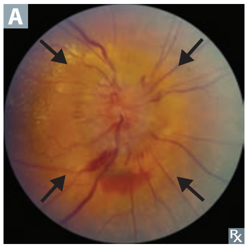

Acute, painless monocular vision loss. Retina cloudy with attenuated vessels and "cherry-red" spot at fovea (center of macula) A. Evaluate for embolic source (eg, carotid artery atherosclerosis, cardiac vegetations, patent foramen ovale).

## Retinitis pigmentosa




Inherited progressive dystrophy of retinal pigmented epithelium and photoreceptors. May be associated with abetalipoproteinemia. Early findings: nyctalopia (night blindness), peripheral vision loss. Fundoscopy may show triad of optic disc pallor, retinal vessel attenuation, and retinal pigmentation with bone spicule-shaped deposits A.

## Papilledema




Optic disc swelling (usually bilateral) due to ↑ ICP (eg, 2° to mass effect). Enlarged blind spot and elevated optic disc with blurred margins A.

## Leukocoria


Loss (whitening) of the red reflex. Important causes in children include retinoblastoma A, congenital cataract.

## Pupillary control

**Miosis**

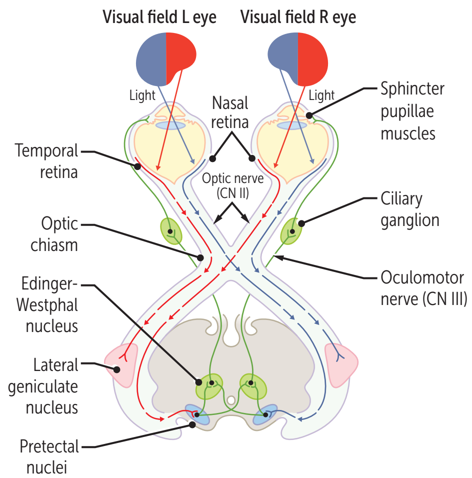
Constriction, parasympathetic:
- 1st neuron: Edinger-Westphal nucleus to ciliary ganglion via CN III
- 2nd neuron: short ciliary nerves to sphincter pupillae muscles

**Short** ciliary nerves **short**en the pupil diameter.

**Pupillary light reflex**

Light in either retina sends a signal via CN II to pretectal nuclei (dashed lines in image) in midbrain that activates bilateral Edinger-Westphal nuclei; pupils constrict bilaterally (direct and consensual reflex).

Result: illumination of 1 eye results in bilateral pupillary constriction.




**Mydriasis**

**D**ilation, sympathetic:
- 1st neuron: hypothalamus to ciliospinal center of Budge (C8–T2)
- 2nd neuron: exit at T1 to superior cervical ganglion (travels along cervical sympathetic chain near lung apex, subclavian vessels)
- 3rd neuron: plexus along internal carotid, through cavernous sinus; enters orbit as long ciliary nerve to pupillary dilator muscles. Sympathetic fibers also innervate smooth muscle of eyelids (minor retractors) and sweat glands of forehead and face.

**Long** ciliary nerves make the pupil diameter **long**er.

**Marcus Gunn pupil**

Also called relative afferent pupillary defect (RAPD). When the light shines into a normal eye, constriction of the ipsilateral (direct reflex) and contralateral eye (consensual reflex) is observed. When the light is then swung to the affected eye, both pupils dilate instead of constrict due to impaired conduction of light signal along the injured optic nerve. Associated with optic neuritis (eg, multiple sclerosis), optic neuropathies (eg, giant cell arteritis).

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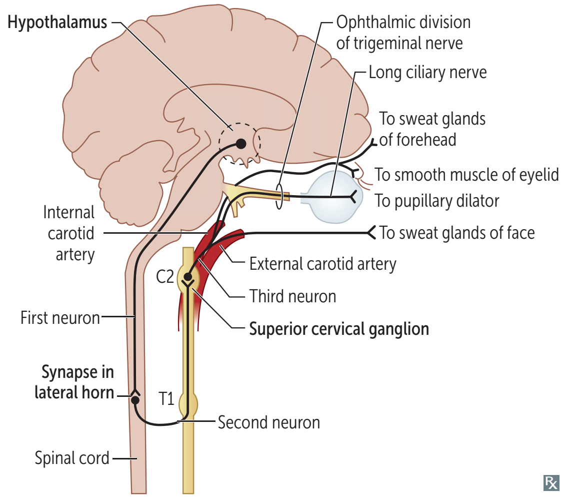
**Horner syndrome**

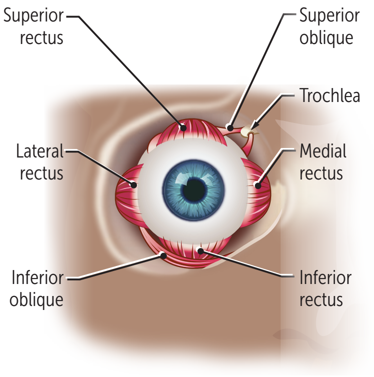
Sympathetic denervation of face →:
- **P**tosis (slight drooping of eyelid: superior tarsal muscle)
- **A**nhidrosis (absence of sweating) and flushing of affected side of face
- **M**iosis (pupil constriction)

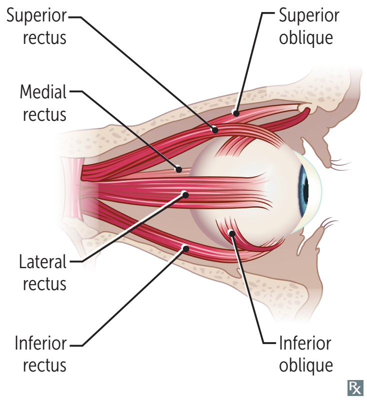
Associated with lesions along the sympathetic chain:
- 1st neuron: pontine hemorrhage, lateral medullary syndrome, spinal cord lesion above T1 (eg, Brown-Séquard syndrome, late-stage syringomyelia)
- 2nd neuron: stellate ganglion compression by Pancoast tumor
- 3rd neuron: carotid dissection (painful); anhidrosis is usually absent

**PAM** is **horn**y (**Horn**er).

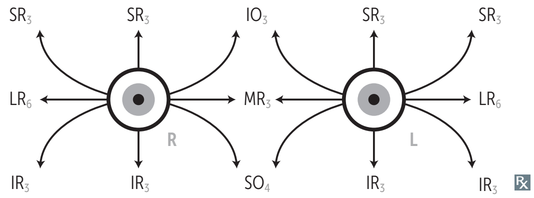


## Ocular motility




CN **VI** innervates the **L**ateral **R**ectus.
CN **IV** innervates the **S**uperior **O**blique.
CN **III** innervates the **R**est.
The "chemical formula" $LR_6SO_4R_3$.





**O**bliques go **O**pposite (left SO and IO tested with patient looking right)
**IOU**: **IO** tested looking **U**p

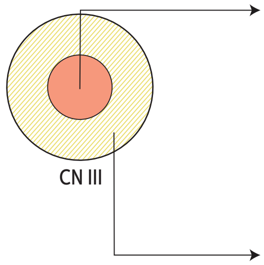
**Blowout fracture**—orbital floor fracture; usually caused by direct trauma to eyeball or intraorbital rim. ↑ risk of IR muscle A and/or orbital fat entrapment. May lead to infraorbital nerve injury

## CN III, IV, VI palsies

### CN III damage

CN III has both motor (central) and parasympathetic (peripheral) components. Common causes include:

- Ischemia → pupil sparing (motor fibers affected more than parasympathetic fibers)
- Uncal herniation → coma
- PCom aneurysm → sudden-onset headache
- Cavernous sinus thrombosis → proptosis, involvement of CNs IV, $V_1/V_2$, VI
- Midbrain stroke → contralateral hemiplegia




Motor output to extraocular muscles—affected primarily by vascular disease (eg, diabetes mellitus: glucose → sorbitol) due to ↓ diffusion of oxygen and nutrients to the interior fibers from compromised vasculature that resides on outside of nerve. Signs: ptosis, "down-and-out" gaze.

Parasympathetic output—fibers on the periphery are first affected by compression (eg, PCom aneurysm, uncal herniation). Signs: diminished or absent pupillary light reflex, "blown pupil" often with "down-and-out" gaze A.

Motor = middle (central)
Parasympathetic = peripheral


### CN IV damage

Pupil is higher in the affected eye B. Characteristic head tilt to contralateral/unaffected side to compensate for lack of intorsion in affected eye.

Can't see the floor with CN IV damage (eg, difficulty going down stairs, reading).


### CN VI damage

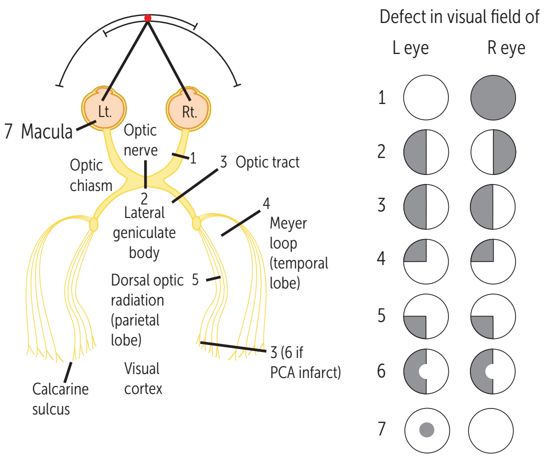
Affected eye unable to abduct C and is displaced medially in primary position of gaze.

## Visual field defects

1. Right anopia (monocular vision loss)
2. Bitemporal hemianopia (pituitary lesion, chiasm)
3. Left homonymous hemianopia
4. Left upper quadrantanopia (right temporal lesion, MCA)
5. Left lower quadrantanopia (right parietal lesion, MCA)
6. Left hemianopia with macular sparing (right occipital lesion, PCA)
7. Central scotoma (eg, macular degeneration)

Meyer loop—lower retina; loops around inferior horn of lateral ventricle.

Dorsal optic radiation—superior retina; takes shortest path via internal capsule.



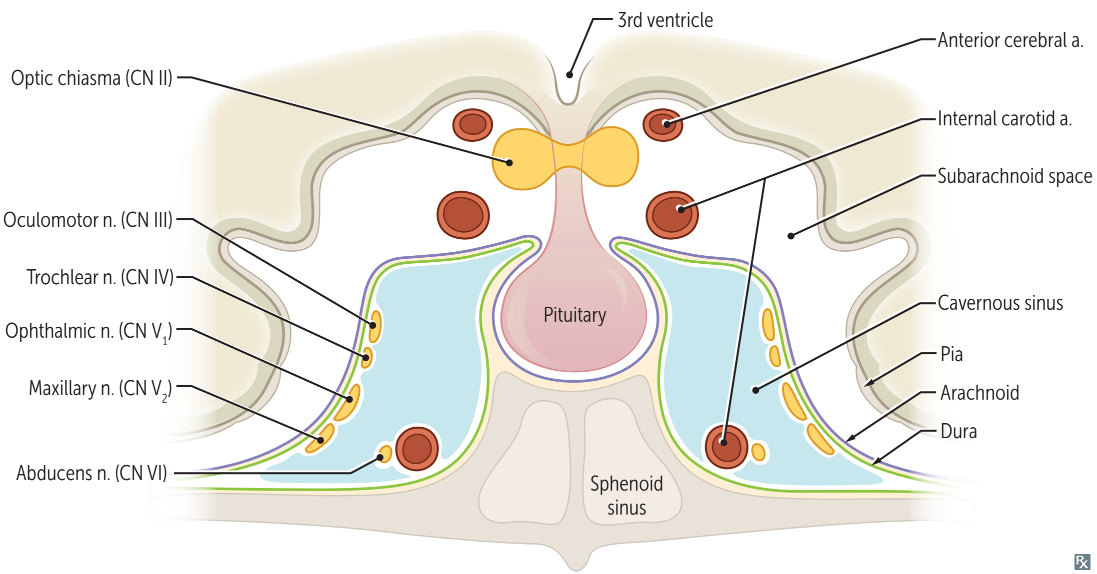

Note: When an image hits 1° visual cortex, it is upside down and left-right reversed.

## Cavernous sinus

Collection of venous sinuses on either side of pituitary. Blood from eye and superficial cortex → cavernous sinus → internal jugular vein.

CNs III, IV, $V_1$, $V_2$, and VI plus postganglionic sympathetic pupillary fibers en route to orbit all pass through cavernous sinus. Cavernous portion of internal carotid artery is also here.

Cavernous sinus syndrome—presents with variable ophthalmoplegia (eg, CN III and CN VI), ↓ corneal sensation, Horner syndrome and occasional decreased maxillary sensation. 2° to pituitary tumor mass effect, carotid-cavernous fistula, or cavernous sinus thrombosis related to infection.



## Internuclear ophthalmoplegia

Medial longitudinal fasciculus (MLF): pair of tracts that interconnect CN VI and CN III nuclei. Coordinates both eyes to move in same horizontal direction. Highly myelinated (must communicate quickly so eyes move at same time). Lesions may be unilateral or bilateral (latter classically seen in multiple sclerosis, stroke).

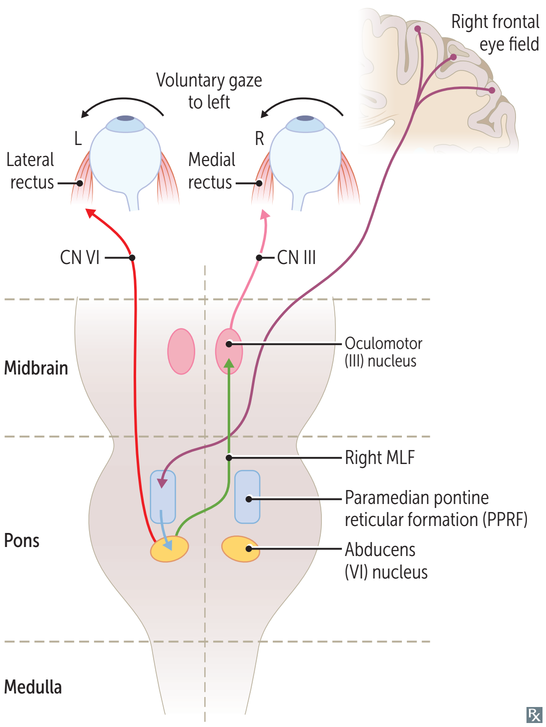
Lesion in MLF = internuclear ophthalmoplegia (INO), a conjugate horizontal gaze palsy. Lack of communication such that when CN VI nucleus activates ipsilateral lateral rectus, contralateral CN III nucleus does not stimulate medial rectus to contract. Abducting eye displays nystagmus (CN VI overfires to stimulate CN III). Convergence normal.

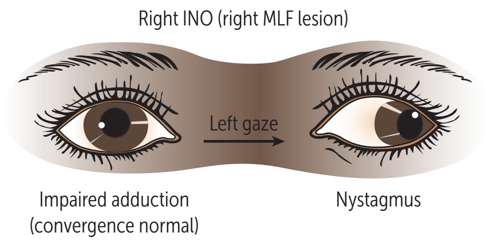
**M**LF in **M**S.

When looking left, the left nucleus of CN VI fires, which contracts the left lateral rectus and stimulates the contralateral (right) nucleus of CN III via the right MLF to contract the right medial rectus.

Directional term (eg, right INO, left INO) refers to the eye that is unable to adduct.

**INO** = **I**psilateral adduction failure, **N**ystagmus **O**pposite.



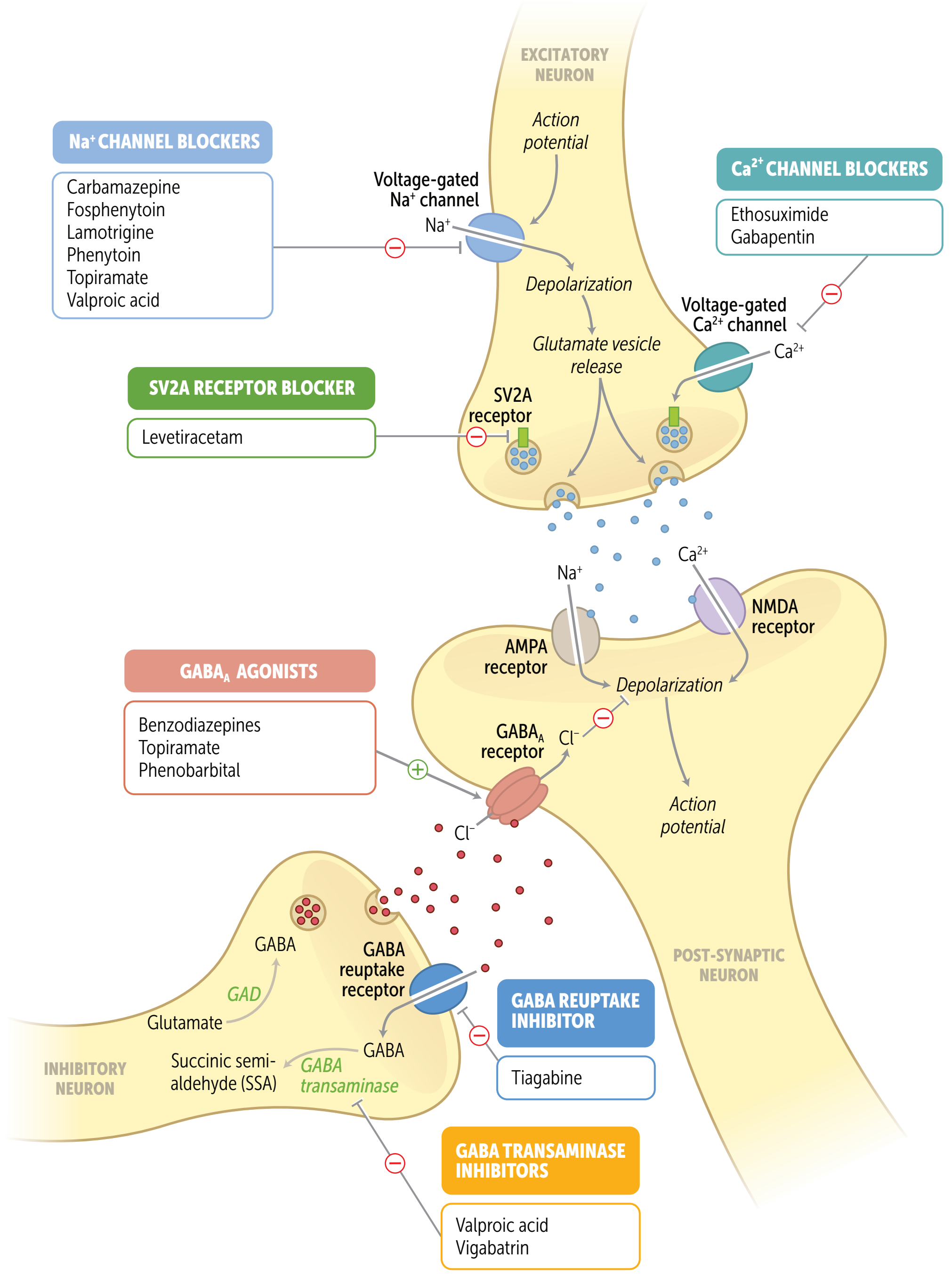
## ▶ NEUROLOGY—PHARMACOLOGY

### Epilepsy therapy

| | PARTIAL (FOCAL)[†] | 1° GENERALIZED: TONIC-CLONIC | 1° GENERALIZED: ABSENCE | STATUS EPILEPTICUS | MECHANISM | SIDE EFFECTS | NOTES |
|---|---|---|---|---|---|---|---|
| **Benzodiazepines** | | | | ** ✓ | ↑ $GABA_A$ action | Sedation, tolerance, dependence, respiratory depression | Also for eclampsia seizures (1st line is $MgSO_4$) |
| **Carbamazepine** | * ✓ | | | | Blocks $Na^+$ channels | Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis (cleft lip/palate, spina bifida), induction of cytochrome P-450, SIADH, SJS | 1st line for trigeminal neuralgia |
| **Ethosuximide** | | | * ✓ | | Blocks thalamic T-type $Ca^{2+}$ channels | EFGHIJ—Ethosuximide causes Fatigue, GI distress, Headache, Itching (and urticaria), SJS | Sucks to have silent (absence) seizures |
| **Gabapentin** | ✓ | | | | Primarily inhibits high-voltage-activated $Ca^{2+}$ channels; designed as GABA analog | Sedation, ataxia | Also used for peripheral neuropathy, postherpetic neuralgia |
| **Lamotrigine** | ✓ | ✓ | ✓ | | Blocks voltage-gated $Na^+$ channels, inhibits the release of glutamate | SJS (must be titrated slowly), hemophagocytic lymphohistiocytosis (black box warning) | |
| **Levetiracetam** | ✓ | ✓ | | | SV2A receptor blocker; may modulate GABA and glutamate release, inhibit voltage-gated $Ca^{2+}$ channels | Neuropsychiatric symptoms (eg, personality change), fatigue, drowsiness, headache | |
| **Phenobarbital** | ✓ | ✓ | | ✓ | ↑ $GABA_A$ action | Sedation, tolerance, dependence, induction of cytochrome P-450, cardiorespiratory depression | 1st line in neonates ("phenobabytal") |
| **Phenytoin, fosphenytoin** | ✓ | | | *** ✓ | Blocks $Na^+$ channels; zero-order kinetics | PPHENYTOIN: cytochrome P-450 induction, Pseudolymphoma, Hirsutism, Enlarged gums, Nystagmus, Yellow-brown skin, Teratogenicity (fetal hydantoin syndrome), Osteopenia, Inhibited folate absorption, Neuropathy. Rare: SJS, DRESS syndrome, drug-induced lupus. Toxicity leads to diplopia, ataxia, sedation. | |
| **Topiramate** | ✓ | ✓ | | | Blocks $Na^+$ channels, ↑ GABA action | Sedation, slow cognition, kidney stones, skinny (weight loss), sight threatened (glaucoma), speech (word-finding) difficulties | Also used for migraine prophylaxis |
| **Valproic acid** | ✓ | * ✓ | ✓ | | ↑ $Na^+$ channel inactivation, ↑ GABA concentration by inhibiting GABA transaminase | VALPPROaTTE: Vomiting, Alopecia, Liver damage (hepatotoxic), Pancreatitis, P-450 inhibition, Rash, Obesity (weight gain), Tremor, Teratogenesis (neural tube defects). Epigastric pain (GI distress). | Also used for myoclonic seizures, bipolar disorder, migraine prophylaxis |
| **Vigabatrin** | ✓ | | | | ↑ GABA. Irreversible GABA transaminase inhibitor | Permanent visual loss (black box warning) | Vision loss with GABA transaminase inhibitor |

* = Common use, ** = 1st line for acute, *** = 1st line for recurrent seizure prophylaxis.
† Includes partial simple/complex and 2° generalized seizures.

## Epilepsy therapy *(continued)*



| | |
|---|---|
| **Barbiturates** | Phenobarbital, pentobarbital, thiopental, secobarbital. |
| MECHANISM | Facilitate $GABA_A$ action by ↑ **duration** of $Cl^-$ channel opening, thus ↓ neuron firing (barbi**durat**es ↑ **durat**ion). |
| CLINICAL USE | Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental). |
| ADVERSE EFFECTS | Respiratory and cardiovascular depression (can be fatal); CNS depression (can be exacerbated by alcohol use); dependence; drug interactions (induces cytochrome P-450).<br>Overdose treatment is supportive (assist respiration and maintain BP).<br>Contraindicated in porphyria. |

| | |
|---|---|
| **Benzodiazepines** | Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam. |
| MECHANISM | Facilitate $GABA_A$ action by ↑ **frequency** of $Cl^-$ channel opening ("**fre**nzodiazepines" ↑ **fre**quency). ↓ REM sleep. Most have long half-lives and active metabolites (exceptions [**ATOM**]: **A**lprazolam, **T**riazolam, **O**xazepam, and **M**idazolam are short acting → higher addictive potential). |
| CLINICAL USE | Anxiety, panic disorder, spasticity, status epilepticus (lorazepam, diazepam, midazolam), eclampsia, detoxification (eg, alcohol withdrawal/DTs; long-acting chlordiazepoxide and diazepam are preferred), night terrors, sleepwalking, general anesthetic (amnesia, muscle relaxation), hypnotic (insomnia). **L**orazepam, **O**xazepam, and **T**emazepam can be used for those with liver disease who drink a **LOT** due to minimal first-pass metabolism. |
| ADVERSE EFFECTS | Dependence, additive CNS depression effects with alcohol and barbiturates (all bind the $GABA_A$ receptor). Less risk of respiratory depression and coma than with barbiturates. Treat overdose with flumazenil (competitive antagonist at GABA benzodiazepine receptor). Can precipitate seizures by causing acute benzodiazepine withdrawal. |

## Insomnia therapy

| AGENT | MECHANISM | ADVERSE EFFECTS | NOTES |
|---|---|---|---|
| **Nonbenzodiazepine hypnotics** | Examples: **Z**olpidem, **Z**aleplon, es**Z**opiclone<br>Act via the $BZ_1$ subtype of GABA receptor | Ataxia, headaches, confusion<br>Cause only modest day-after psychomotor depression and few amnestic effects (vs older sedative-hypnotics) | These **ZZZ**s put you to sleep<br>Short duration due to rapid metabolism by liver enzymes; effects reversed by flumazenil<br>↓ dependency risk and ↓ sleep cycle disturbance (vs benzodiazepine hypnotics) |
| **Suvorexant** | **Orex**in (hypocretin) receptor **ant**agonist | CNS depression (somnolence), headache, abnormal sleep-related activities | Contraindications: narcolepsy, combination with strong CYP3A4 inhibitors<br>Not recommended in patients with liver disease<br>Limited risk of dependency |
| **Ramelteon** | **Mel**atonin receptor agonist: binds MT1 and MT2 in suprachiasmatic nucleus | Dizziness, nausea, fatigue, headache | No known risk of dependency |

## Triptans

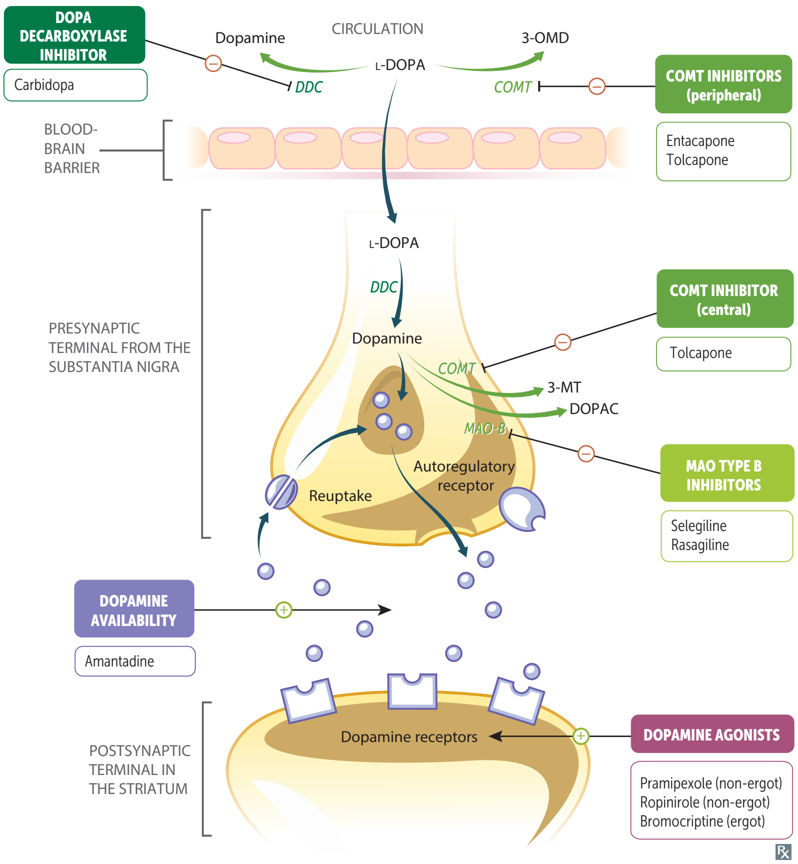
**Suma**trip**tan**

| | | |
|---|---|---|
| MECHANISM | $5\text{-HT}_{1B/1D}$ agonists. Inhibit trigeminal nerve activation, prevent vasoactive peptide release, induce vasoconstriction. | A **sumo** wrestler **trips and** falls on their **head**. |
| CLINICAL USE | Acute migraine, cluster **head**ache attacks. | |
| ADVERSE EFFECTS | Coronary vasospasm (contraindicated in patients with CAD or vasospastic angina), mild paresthesia, serotonin syndrome (in combination with other 5-HT agonists). | |

**Parkinson disease therapy**

The most effective treatments are non-ergot dopamine agonists which are usually started in younger patients, and Levodopa (with carbidopa) which is usually started in older patients. Deep brain stimulation of the STN or GPi may be helpful in advanced disease.

| STRATEGY | AGENTS |
|---|---|
| **Dopamine agonists** | Non-ergot (preferred)—pramipexole, ropinirole; toxicity includes nausea, impulse control disorder (eg, gambling), postural hypotension, hallucinations, confusion.<br>Ergot—bromocriptine rarely used due to toxicity. |
| **↑ dopamine availability** | Amantadine (↑ dopamine release and ↓ dopamine reuptake); toxicity = peripheral edema, livedo reticularis, ataxia. |
| **↑ L-DOPA availability** | Agents prevent peripheral (pre-BBB) L-DOPA degradation → ↑ L-DOPA entering CNS → ↑ central L-DOPA available for conversion to dopamine.<br>▪ Levodopa (L-DOPA)/carbidopa—carbidopa blocks peripheral conversion of L-DOPA to dopamine by inhibiting DOPA decarboxylase. Also reduces side effects of peripheral L-DOPA conversion into dopamine (eg, nausea, vomiting).<br>▪ Entacapone and tolcapone prevent peripheral L-DOPA degradation to 3-O-methyldopa (3-OMD) by inhibiting COMT. Used in conjunction with levodopa. |
| **Prevent dopamine breakdown** | Agents act centrally (post-BBB) to inhibit breakdown of dopamine.<br>▪ Selegiline, rasagiline—block conversion of dopamine into DOPAC by selectively inhibiting MAO-B.<br>▪ Tolcapone—crosses BBB and blocks conversion of dopamine to 3-methoxytyramine (3-MT) in the brain by inhibiting central COMT. |
| **Curb excess cholinergic activity** | **Benz**tropine, **tri**hexyphenidyl (**A**ntimuscarinic; improves tremor and rigidity but has little effect on bradykinesia in **Park**inson disease). **Tri Park**ing my Mercedes-**Benz**. |



## Carbidopa/levodopa

| | |
|---|---|
| MECHANISM | ↑ dopamine in brain. Unlike dopamine, L-DOPA can cross blood-brain barrier and is converted by dopa decarboxylase in the CNS to dopamine. Carbidopa, a peripheral DOPA decarboxylase inhibitor, is given with L-DOPA to ↑ bioavailability of L-DOPA in the brain and to limit peripheral side effects. |
| CLINICAL USE | Parkinson disease. |
| ADVERSE EFFECTS | Nausea, hallucinations, postural hypotension. With progressive disease, L-DOPA can lead to "on-off" phenomenon with improved mobility during "on" periods, then impaired motor function during "off" periods when patient responds poorly to L-DOPA or medication wears off. |

## Selegiline, rasagiline

| | |
|---|---|
| MECHANISM | Selectively inhibit MAO-B (metabolize dopamine) → ↑ dopamine availability.<br>**Sele**giline **sele**ctively inhibits MAO-**B** and is more commonly found in the **B**rain than in the periphery. |
| CLINICAL USE | Adjunctive agent to L-DOPA in treatment of Parkinson disease. |
| ADVERSE EFFECTS | May enhance adverse effects of L-DOPA. |

## Neurodegenerative disease therapy

| DISEASE | AGENT | MECHANISM | NOTES |
|---|---|---|---|
| **Alzheimer disease** | **Done**pezil, **riva**stigmine, **gala**ntamine | AChE inhibitor | 1st-line treatment<br>Adverse effects: nausea, dizziness, insomnia. Contraindicated in patients with cardiac conduction abnormalities.<br>**Dona Riva** dances at the **gala** |
| | Memantine | NMDA receptor antagonist; helps prevent excitotoxicity (mediated by $Ca^{2+}$) | Used for moderate to advanced dementia<br>Adverse effects: dizziness, confusion, hallucinations |
| **Amyotrophic lateral sclerosis** | Riluzole | ↓ neuron glutamate excitotoxicity | ↑ survival<br>Treat **Lou** Gehrig disease with ri**Lou**zole |
| **Huntington disease** | Tetrabenazine | Inhibit vesicular monoamine transporter (VMAT) → ↓ dopamine vesicle packaging and release | May be used for Huntington chorea and tardive dyskinesia |

**Anesthetics—general principles**

CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported.
Drugs with ↓ solubility in blood = rapid induction and recovery times.
Drugs with ↑ solubility in lipids = ↑ potency.
**MAC** = **M**inimum **A**lveolar **C**oncentration (of inhaled anesthetic) required to prevent 50% of subjects from moving in response to noxious stimulus (eg, skin incision). Potency = 1/MAC.
Examples: nitrous oxide ($N_2O$) has ↓ blood and lipid solubility, and thus fast induction and low potency. Halothane has ↑ lipid and blood solubility, and thus high potency and slow induction.

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**Inhaled anesthetics**

Desflur**ane**, haloth**ane**, enflur**ane**, isoflur**ane**, sevoflur**ane**, methoxyflur**ane**, $N_2O$.

MECHANISM: Mechanism unknown.

EFFECTS: Myocardial depression, respiratory depression, postoperative nausea/vomiting, ↑ cerebral blood flow and ICP, ↓ cerebral metabolic demand.

ADVERSE EFFECTS: **H**epatotoxicity (**h**alothane), **neph**rotoxicity (**meth**oxyflurane), proconvulsant (**e**nflurane, **e**pileptogenic), expansio**n** of trapped gas in a body cavity (**N**$_2$O).

Malignant hyperthermia—rare, life-threatening condition in which inhaled anesthetics or succinylcholine induce severe muscle contractions and hyperthermia. Susceptibility is often inherited as autosomal dominant with variable penetrance. Mutations in ryanodine receptor (*RYR1*) cause ↑ $Ca^{2+}$ release from sarcoplasmic reticulum.
Treatment: dantrolene (a ryanodine receptor antagonist).

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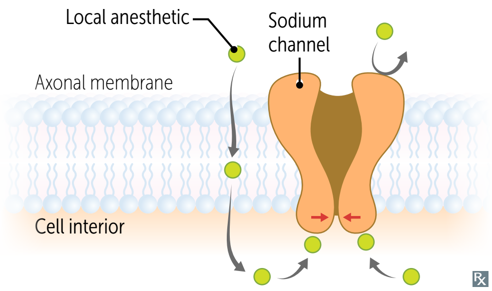
**Intravenous anesthetics**

| AGENT | MECHANISM | ANESTHESIA USE | NOTES |
|---|---|---|---|
| **Thiopental** | Facilitates $GABA_A$ (barbiturate) | Anesthesia induction, short surgical procedures | ↓ cerebral blood flow. High lipid solubility<br>Effect terminated by rapid redistribution into tissue, fat |
| **Midazolam** | Facilitates $GABA_A$ (benzodiazepine) | Procedural sedation (eg, endoscopy), anesthesia induction | May cause severe postoperative respiratory depression, ↓ BP, anterograde amnesia |
| **Propofol** | Potentiates $GABA_A$ | Rapid anesthesia induction, short procedures, ICU sedation | May cause respiratory depression, ↓ BP |
| **Ketamine** | NMDA receptor antagonist | Dissociative anesthesia<br>Sympathomimetic | ↑ cerebral blood flow<br>Emergence reaction possible with disorientation, hallucination, vivid dreams |

## Local anesthetics

Esters—procaine, tetracaine, benzocaine, chloroprocaine.
Amides—lidocaine, mepivacaine, bupivacaine, ropivacaine, prilocaine (amides have 2 i's in name).




| | |
|---|---|
| MECHANISM | Block neurotransmission via binding to voltage-gated $Na^+$ channels on inner portion of the channel along nerve fibers. Most effective in rapidly firing neurons. 3° amine local anesthetics penetrate membrane in uncharged form, then bind to ion channels as charged form.<br>Can be given with vasoconstrictors (usually epinephrine) to enhance block duration of action by ↓ systemic absorption.<br>In infected (acidic) tissue, alkaline anesthetics are charged and cannot penetrate membrane effectively → need more anesthetic.<br>Order of loss: (1) pain, (2) temperature, (3) touch, (4) pressure. |
| CLINICAL USE | Minor surgical procedures, spinal anesthesia. If allergic to esters, give amides. |
| ADVERSE EFFECTS | CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension, hypotension, arrhythmias (cocaine), methemoglobinemia (benzocaine, prilocaine). |

## Neuromuscular blocking drugs

Muscle paralysis in surgery or mechanical ventilation. Selective for Nm nicotinic receptors at neuromuscular junction but not autonomic Nn receptors.

### Depolarizing neuromuscular blocking drugs

Succinylcholine—strong ACh receptor agonist; produces sustained depolarization and prevents muscle contraction.
Reversal of blockade:
- Phase I (prolonged depolarization)—no antidote. Block potentiated by cholinesterase inhibitors.
- Phase II (repolarized but blocked; ACh receptors are available, but desensitized)—may be reversed with cholinesterase inhibitors.

Complications include hypercalcemia, hyperkalemia, malignant hyperthermia. ↑ risk of prolonged muscle paralysis in patients with pseudocholinesterase deficiency.

### Nondepolarizing neuromuscular blocking drugs

Atracurium, cisatracurium, pancuronium, rocuronium, tubocurarine, vecuronium—competitive ACh antagonist.
Reversal of blockade—sugammadex or cholinesterase inhibitors (eg, neostigmine, edrophonium). Anticholinergics (eg, atropine, glycopyrrolate) are given with cholinesterase inhibitors to prevent muscarinic effects (eg, bradycardia).

## Spasmolytics, antispasmodics

| DRUG | MECHANISM | CLINICAL USE | NOTES |
|---|---|---|---|
| **Baclofen** | $GABA_B$ receptor agonist in spinal cord | Muscle spasticity, dystonia, multiple sclerosis | Acts on the **back** (spinal cord) |
| **Cyclobenzaprine** | Acts within CNS, mainly at the brain stem | Muscle spasticity | **C**entrally acting<br>Structurally related to TCAs<br>May cause anticholinergic side effects, sedation |
| **Dantrolene** | Prevents release of $Ca^{2+}$ from sarcoplasmic reticulum of skeletal muscle by inhibiting the ryanodine receptor | Malignant hyperthermia (toxicity of inhaled anesthetics and succinylcholine) and neuroleptic malignant syndrome (toxicity of antipsychotic drugs) | Acts **d**irectly on muscle |
| **Tizanidine** | $\alpha_2$ agonist, acts centrally | Muscle spasticity, multiple sclerosis, ALS, cerebral palsy | |

## Opioid analgesics

| | |
|---|---|
| MECHANISM | Act as agonists at opioid receptors ($\mu$ = β-endorphin, $\delta$ = enkephalin, $\kappa$ = dynorphin) to modulate synaptic transmission—close presynaptic $Ca^{2+}$ channels, open postsynaptic $K^+$ channels → ↓ synaptic transmission. Inhibit release of ACh, norepinephrine, 5-HT, glutamate, substance P. |
| EFFICACY | Full agonist: morphine, heroin, meperidine (long acting), methadone, codeine (prodrug; activated by CYP2D6), fentanyl.<br>Partial agonist: buprenorphine.<br>Mixed agonist/antagonist: nalbuphine, pentazocine, butorphanol.<br>Antagonist: naloxone, naltrexone, methylnaltrexone. |
| CLINICAL USE | Moderate to severe or refractory pain, diarrhea (loperamide, diphenoxylate), acute pulmonary edema, maintenance programs for opiate use disorder (methadone, buprenorphine + naloxone), neonatal abstinence syndrome (methadone, morphine). |
| ADVERSE EFFECTS | Nausea, vomiting, pruritus (histamine release), opiate use disorder, respiratory depression, constipation, sphincter of Oddi spasm, miosis (except meperidine → mydriasis), additive CNS depression with other drugs. Tolerance does not develop to miosis and constipation. Treat toxicity with naloxone (competitive opioid receptor antagonist) and prevent relapse with naltrexone once detoxified. |

## Mixed agonist and antagonist opioid analgesics

| DRUG | MECHANISM | CLINICAL USE | NOTES |
|---|---|---|---|
| **Pentazocine** | κ-opioid receptor agonist and μ-opioid receptor weak antagonist or partial agonist. | Analgesia for moderate to severe pain. | Can cause opioid withdrawal symptoms if patient is also taking full opioid agonist (due to competition for opioid receptors). |
| **Butorphanol** | κ-opioid receptor agonist and μ-opioid receptor partial agonist. | Severe pain (eg, migraine, labor). | Causes less respiratory depression than full opioid agonists. Use with full opioid agonist can precipitate withdrawal. Not easily reversed with naloxone. |

## Tramadol

| | | |
|---|---|---|
| MECHANISM | Very weak opioid agonist; also inhibits the reuptake of norepinephrine and serotonin. | Tramadol is a slight opioid agonist, and a serotonin and norepinephrine reuptake inhibitor. It is used for stubborn pain, but can lower seizure threshold, and may cause serotonin syndrome. |
| CLINICAL USE | Chronic pain. | |
| ADVERSE EFFECTS | Similar to opioids; decreases seizure threshold; serotonin syndrome. | |

## Glaucoma therapy

↓ IOP via ↓ amount of aqueous humor (inhibit synthesis/secretion or ↑ drainage).
BAD humor may not be politically correct.

| DRUG CLASS | EXAMPLES | MECHANISM | ADVERSE EFFECTS |
|---|---|---|---|
| **β-blockers** | Timolol, betaxolol, carteolol | ↓ aqueous humor synthesis | No pupillary or vision changes |
| **α-agonists** | Epinephrine ($\alpha_1$), apraclonidine, brimonidine ($\alpha_2$) | ↓ aqueous humor synthesis via vasoconstriction (epinephrine)<br>↓ aqueous humor synthesis (apraclonidine, brimonidine) | Mydriasis ($\alpha_1$); do not use in closed-angle glaucoma<br>Blurry vision, ocular hyperemia, foreign body sensation, ocular allergic reactions, ocular pruritus |
| **Diuretics** | Acetazolamide | ↓ aqueous humor synthesis via inhibition of carbonic anhydrase | No pupillary or vision changes |
| **Prostaglandins** | Bimatoprost, latanoprost ($PGF_{2\alpha}$) | ↑ outflow of aqueous humor via ↓ resistance of flow through uveoscleral pathway | Darkens color of iris (browning), eyelash growth |
| **Cholinomimetics ($M_3$)** | Direct: pilocarpine, carbachol<br>Indirect: physostigmine, echothiophate | ↑ outflow of aqueous humor via contraction of ciliary muscle and opening of trabecular meshwork<br>Use pilocarpine in acute angle closure glaucoma—very effective at opening meshwork into canal of Schlemm | Miosis (contraction of pupillary sphincter muscles) and cyclospasm (contraction of ciliary muscle) |

NOTES

HIGH-YIELD PRINCIPLES IN

# Psychiatry

*"Words of comfort, skillfully administered, are the oldest therapy known to man."*

—Louis Nizer

*"Even a happy life cannot be without a measure of darkness, and the word happy would lose its meaning if it were not balanced by sadness."*

—Carl G. Jung

*"The sorrow which has no vent in tears may make other organs weep."*

—Henry Maudsley

*"I have schizophrenia. I am not schizophrenia. I am not my mental illness. My illness is a part of me."*

—Jonathan Harnisch

This chapter encompasses overlapping areas in psychiatry, psychology, sociology, and psychopharmacology. High-yield topics include schizophrenia, mood disorders, eating disorders, personality disorders, somatic symptom disorders, substance use disorders, and antipsychotic agents. Know the DSM-5 criteria for diagnosing common psychiatric disorders.

## ▶ PSYCHIATRY—PSYCHOLOGY

| | | |
|---|---|---|
| **Classical conditioning** | Learning in which a natural response (salivation) is elicited by a conditioned, or learned, stimulus (bell) that previously was presented in conjunction with an unconditioned stimulus (food). | Usually elicits **involuntary** responses. Pavlov's classical experiments with dogs—ringing the bell provoked salivation. |

| | | |
|---|---|---|
| **Operant conditioning** | Learning in which a particular action is elicited because it produces a punishment or reward. Usually elicits **voluntary** responses. | |
| **Reinforcement** | Target behavior (response) is followed by desired reward (positive reinforcement) or removal of aversive stimulus (negative reinforcement). | Skinner operant conditioning quadrants: |
| **Punishment** | Repeated application of aversive stimulus (positive punishment) or removal of desired reward (negative punishment) to extinguish unwanted behavior. | |
| **Extinction** | Discontinuation of reinforcement (positive or negative) eventually eliminates behavior. Can occur in operant or classical conditioning. | |

| | Increase behavior | Decrease behavior |
|---|---|---|
| Add a stimulus | Positive reinforcement | Positive punishment |
| Remove a stimulus | Negative reinforcement | Negative punishment |

### Transference and countertransference

| | |
|---|---|
| **Transference** | Patient projects feelings about formative or other important persons onto physician (eg, psychiatrist is seen as parent). |
| **Countertransference** | Physician projects feelings about formative or other important persons onto patient (eg, patient reminds physician of younger sibling). |

**Ego defenses** Thoughts and behaviors (voluntary or involuntary) used to resolve conflict and prevent undesirable feelings (eg, anxiety, depression).

| IMMATURE DEFENSES | DESCRIPTION | EXAMPLE |
|---|---|---|
| **Acting out** | Subconsciously coping with stressors or emotional conflict using actions rather than reflections or feelings. | A patient skips therapy appointments after deep discomfort from dealing with his past. |
| **Denial** | Avoiding the awareness of some painful reality. | A patient with cancer plans a full-time work schedule despite being warned of significant fatigue during chemotherapy. |
| **Displacement** | Redirection of emotions or impulses to a neutral person or object (vs projection). | After being reprimanded by her principal, a frustrated teacher returns home and criticizes her wife's cooking instead of confronting the principal directly. |
| **Dissociation** | Temporary, drastic change in personality, memory, consciousness, or motor behavior to avoid emotional stress. Patient has incomplete or no memory of traumatic event. | A survivor of sexual abuse sees the abuser and suddenly becomes numb and detached. |

### Ego defenses *(continued)*

| IMMATURE DEFENSES | DESCRIPTION | EXAMPLE |
|---|---|---|
| **Fixation** | Partially remaining at a more childish level of development (vs regression). | A surgeon throws a tantrum in the operating room because the last case ran very late. |
| **Idealization** | Expressing extremely positive thoughts of self and others while ignoring negative thoughts. | A patient boasts about his physician and his accomplishments while ignoring any flaws. |
| **Identification** | Largely unconscious assumption of the characteristics, qualities, or traits of another person or group. | A resident starts putting her stethoscope in her pocket like her favorite attending, instead of wearing it around her neck like before. |
| **Intellectualization** | Using facts and logic to emotionally distance oneself from a stressful situation. | A patient diagnosed with cancer discusses the pathophysiology of the disease. |
| **Isolation (of affect)** | Separating feelings from ideas and events. | Describing murder in graphic detail with no emotional response. |
| **Passive aggression** | Demonstrating hostile feelings in a nonconfrontational manner; showing indirect opposition. | A disgruntled employee is repeatedly late to work, but won't admit it is a way to get back at the manager. |
| **Projection** | Attributing an unacceptable internal impulse to an external source (vs displacement). | A man who wants to cheat on his wife accuses his wife of being unfaithful. |
| **Rationalization** | Asserting plausible explanations for events that actually occurred for other reasons, usually to avoid self-blame. | An employee who was recently fired claims that the job was not important anyway. |
| **Reaction formation** | Replacing a warded-off idea or feeling with an emphasis on its opposite (vs sublimation). | A stepfather treats a child he resents with excessive nurturing and overprotection. |
| **Regression** | Involuntarily turning back the maturational clock to behaviors previously demonstrated under stress (vs fixation). | A previously toilet-trained child begins bedwetting again following the birth of a sibling. |
| **Repression** | Involuntarily withholding an idea or feeling from conscious awareness (vs suppression). | A 20-year-old does not remember going to counseling during his parents' divorce 10 years earlier. |
| **Splitting** | Believing that people are either all good or all bad at different times due to intolerance of ambiguity. Common in borderline personality disorder. | A patient says that all the nurses are cold and insensitive, but the physicians are warm and friendly. |
| MATURE DEFENSES | | |
| **Sublimation** | Replacing an unacceptable wish with a course of action that is similar to the wish but socially acceptable (vs reaction formation). | A teenager's aggression toward her parents because of their high expectations is channeled into excelling in sports. |
| **Altruism** | Alleviating negative feelings via unsolicited generosity, which provides gratification (vs reaction formation). | A mafia boss makes a large donation to charity. |
| **Suppression** | Intentionally withholding an idea or feeling from conscious awareness (vs repression); temporary. | An athlete focuses on other tasks to prevent worrying about an important upcoming match. |
| **Humor** | Lightheartedly expressing uncomfortable feelings to shift the internal focus away from the distress. | A nervous medical student jokes about the boards. |
| | Mature adults wear a SASH. | |

**Grief**

The five stages of grief per the Kübler-Ross model are denial, anger, bargaining, depression, and acceptance (may occur in any order). Other common grief symptoms include shock, guilt, sadness, anxiety, yearning, and somatic symptoms that usually occur in waves. Auditory or visual hallucinations can occur in the context of normal bereavement (eg, hearing the deceased speaking). Duration varies widely. Persistent complex bereavement disorder is diagnosed if severe grief interferes with functioning for > 12 months.

**Normal infant and child development**

Milestone dates are ranges that have been approximated and vary by source. Children not meeting milestones may need assessment for potential developmental delay.

| AGE | MOTOR | SOCIAL | VERBAL/COGNITIVE |
|---|---|---|---|
| **Infant** | **Parents** | **Start** | **Observing,** |
| 0–12 mo | Primitive reflexes disappear—Moro (by 3 mo), rooting (by 4 mo), palmar (by 6 mo), Babinski (by 12 mo)<br>Posture—lifts head up prone (by 1 mo), rolls and sits (by 6 mo), crawls (by 8 mo), stands (by 10 mo), walks (by 12–18 mo)<br>Picks—passes toys hand to hand (by 6 mo), Pincer grasp (by 10 mo)<br>Points to objects (by 12 mo) | Social smile (by 2 mo)<br>Stranger anxiety (by 6 mo)<br>Separation anxiety (by 9 mo) | Orients—first to voice (by 4 mo), then to name and gestures (by 9 mo)<br>Object permanence (by 9 mo)<br>Oratory—says “mama” and “dada” (by 10 mo) |
| **Toddler** | **Child** | **Rearing** | **Working,** |
| 12–36 mo | Cruises, takes first steps (by 12 mo)<br>Climbs stairs (by 18 mo)<br>Cubes stacked (number) = age (yr) × 3<br>Cutlery—feeds self with fork and spoon (by 20 mo)<br>Kicks ball (by 24 mo) | Recreation—parallel play (by 24–36 mo)<br>Rapprochement—moves away from and returns to parent (by 24 mo)<br>Realization—core gender identity formed (by 36 mo) | Words—uses 50-200 words (by 2 yr), uses 300+ words (by 3 yr) |
| **Preschool** | **Don’t** | **Forget, they’re still** | **Learning!** |
| 3–5 yr | Drive—tricycle (3 wheels at 3 yr)<br>Drawings—copies line or circle, stick figure (by 4 yr)<br>Dexterity—hops on one foot by 4 yr (“4 on one foot”), uses buttons or zippers, grooms self (by 5 yr) | Freedom—comfortably spends part of day away from parent (by 3 yr)<br>Friends—cooperative play, has imaginary friends (by 4 yr) | Language—understands 1000 (3 zeros) words (by 3 yr), uses complete sentences and prepositions (by 4 yr)<br>Legends—can tell detailed stories (by 4 yr) |

## ▸ PSYCHIATRY—PATHOLOGY

### Infant deprivation effects

Long-term deprivation of affection results in:
- Failure to thrive
- Poor language/socialization skills
- Lack of basic trust
- Reactive attachment disorder (infant withdrawn/unresponsive to comfort)
- Disinhibited social engagement (child indiscriminately attaches to strangers)

Deprivation for > 6 months can lead to irreversible changes.
Severe deprivation can result in infant death.

### Child abuse

| | Physical abuse | Sexual abuse | Emotional abuse |
|---|---|---|---|
| SIGNS | Nonaccidental trauma (eg, fractures, bruises, burns). Injuries often in different stages of healing or in patterns resembling possible implements of injury. Includes abusive head trauma (shaken baby syndrome), characterized by subdural hematomas or retinal hemorrhages.<br>Caregivers may delay seeking medical attention for the child or provide explanations inconsistent with the child's developmental stage or pattern of injury. | STIs, UTIs, and genital, anal, or oral trauma. Most often, there are no physical signs; sexual abuse should not be excluded from a differential diagnosis in the absence of physical trauma.<br>Children often exhibit sexual knowledge or behavior incongruent with their age. | Babies or young children may lack a bond with the caregiver but are overly affectionate with less familiar adults. They may be aggressive toward children and animals or unusually anxious.<br>Older children are often emotionally labile and prone to angry outbursts. They may distance themselves from caregivers and other children. They can experience vague somatic symptoms for which a medical cause cannot be found. |
| EPIDEMIOLOGY | 40% of deaths related to child abuse or neglect occur in children < 1 year old. | Peak incidence 9–12 years old. | ~80% of young adult victims of child emotional abuse meet the criteria for ≥ 1 psychiatric illness by age 21. |

### Child neglect

Failure to provide a child with adequate food, shelter, supervision, education, and/or affection. Most common form of child maltreatment. Signs: poor hygiene, malnutrition, withdrawal, impaired social/emotional development, failure to thrive.
As with child abuse, suspected child neglect must be reported to local child protective services.

### Vulnerable child syndrome

Parents perceive the child as especially susceptible to illness or injury (vs factitious disorder imposed on another). Usually follows a serious illness or life-threatening event. Can result in missed school or overuse of medical services.

## Childhood and early-onset disorders

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| **Attention-deficit hyperactivity disorder** | Onset before age 12. ≥ 6 months of limited attention span and/or poor impulse control. Characterized by hyperactivity, impulsivity, and/or inattention in ≥ 2 settings (eg, school, home, places of worship). Normal intelligence, but commonly coexists with difficulties in school. Often persists into adulthood. Commonly coexists with oppositional defiant disorder. Treatment: stimulants (eg, methylphenidate) +/– behavioral therapy; alternatives include atomoxetine and $\alpha_2$-agonists (eg, clonidine, guanfacine). |
| **Autism spectrum disorder** | Onset in early childhood. Social and communication deficits, repetitive/ritualized behaviors, restricted interests. May be accompanied by intellectual disability and/or above average abilities in specific skills (eg, music). More common in males. Associated with ↑ head and/or brain size. |
| **Conduct disorder** | Repetitive, pervasive behavior violating societal norms or the basic rights of others (eg, aggression toward people and animals, destruction of property, theft). After age 18, often reclassified as antisocial personality disorder. Treatment: psychotherapy (eg, cognitive behavioral therapy [CBT]). |
| **Disruptive mood dysregulation disorder** | Onset before age 10. Severe, recurrent temper outbursts out of proportion to situation. Child is constantly angry and irritable between outbursts. Treatment: CBT, stimulants, antipsychotics. |
| **Intellectual disability** | Global cognitive deficits (vs specific learning disorder) that affect reasoning, memory, abstract thinking, judgment, language, learning. Adaptive functioning is impaired, leading to major difficulties with education, employment, communication, socialization, independence. Treatment: psychotherapy, occupational therapy, special education. |
| **Intermittent explosive disorder** | Onset after age 6. Recurrent verbal or physical outbursts representing a failure to control aggressive impulses. Outbursts are out of proportion to provocation and may lead to legal, financial, or social consequences. Episodes are not premeditated and last < 30 minutes. Treatment: psychotherapy, SSRIs. |
| **Oppositional defiant disorder** | Pattern of anger and irritability with argumentative, vindictive, and defiant behavior toward authority figures lasting ≥ 6 months. Treatment: psychotherapy (eg, CBT). |
| **Selective mutism** | Onset before age 5. Anxiety disorder lasting ≥ 1 month involving refraining from speech in certain situations despite speaking in other, usually more comfortable situations. Development (eg, speech and language) not typically impaired. Interferes with social, academic, and occupational tasks. Commonly coexists with social anxiety disorder. Treatment: behavioral, family, and play therapy; SSRIs. |
| **Separation anxiety disorder** | Overwhelming fear of separation from home or attachment figure lasting ≥ 4 weeks. Can be normal behavior up to age 3–4. May lead to factitious physical complaints to avoid school. Treatment: CBT, play therapy, family therapy. |
| **Specific learning disorder** | Onset during school-age years. Inability to acquire or use information from a specific subject (eg, math, reading, writing) near age-expected proficiency for ≥ 6 months despite focused intervention. General functioning and intelligence are normal (vs intellectual disability). Treatment: academic support, counseling, extracurricular activities. |
| **Tourette syndrome** | Onset before age 18. Sudden, recurrent, nonrhythmic, stereotyped motor and vocal tics that persist for > 1 year. Coprolalia (involuntary obscene speech) found in some patients. Associated with OCD and ADHD. Treatment: psychoeducation, behavioral therapy. For intractable and distressing tics: tetrabenazine, antipsychotics, $\alpha_2$-agonists. |

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| **Orientation** | Patients' ability to know the date and time, where they are, and who they are (order of loss: time → place → person). Common causes of loss of orientation: alcohol, drugs, fluid/electrolyte imbalance, head trauma, hypoglycemia, infection, nutritional deficiencies, hypoxia. |

### Amnesias

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| **Retrograde amnesia** | Inability to remember things that occurred **before** a CNS insult. |
| **Anterograde amnesia** | Inability to remember things that occurred **a**fter a CNS insult (↓ acquisition of new memory). |
| **Korsakoff syndrome** | Amnesia (anterograde > retrograde) and disorientation caused by vitamin $B_1$ deficiency. Associated with disruption and destruction of the limbic system, especially mammillary bodies and anterior thalamus. Seen in chronic alcohol use as a late neuropsychiatric manifestation of Wernicke encephalopathy. Confabulations are characteristic. |

### Dissociative disorders

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| **Depersonalization/derealization disorder** | Persistent feelings of detachment or estrangement from one's own body, thoughts, perceptions, and actions (depersonalization) or one's environment (derealization). Intact reality testing (vs psychosis). |
| **Dissociative amnesia** | Inability to recall important personal information, usually following severe trauma or stress. May be accompanied by dissociative fugue (abrupt, unexpected travelling away from home). |
| **Dissociative identity disorder** | Formerly called multiple personality disorder. Presence of ≥ 2 distinct identities or personality states, typically with distinct memories and patterns of behavior. More common in females. Associated with history of sexual abuse, PTSD, depression, substance use, borderline personality disorder, somatic symptom disorders. |

**Delirium**

"Waxing and waning" level of consciousness with acute onset, ↓ attention span, ↓ level of arousal. Characterized by disorganized thinking, hallucinations (often visual), misperceptions (eg, illusions), disturbance in sleep-wake cycle, cognitive dysfunction, agitation. Reversible.

Usually 2° to other identifiable illness (eg, CNS disease, infection, trauma, substance use/withdrawal, metabolic/electrolyte disturbances, hemorrhage, urinary/fecal retention), or medications (eg, anticholinergics), especially in the elderly.

Most common presentation of altered mental status in inpatient setting, especially in the ICU or during prolonged hospital stays.

Deli**rium** = changes in senso**rium**.

EEG may show diffuse background rhythm slowing.

Treatment: identification and management of underlying condition. Orientation protocols (eg, keeping a clock or calendar nearby), ↓ sleep disturbances, and ↑ cognitive stimulation to manage symptoms. Antipsychotics (eg, haloperidol) as needed. Avoid unnecessary restraints and drugs that may worsen delirium (eg, anticholinergics, benzodiazepines, opioids).

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| **Psychosis** | Distorted perception of reality characterized by delusions, hallucinations, and/or disorganized thought/speech. Can occur in patients with medical illness, psychiatric illness, or both. |
| **Delusions** | False, fixed, idiosyncratic beliefs that persist despite evidence to the contrary and are not typical of a patient's culture or religion (eg, a patient who believes that others are reading his thoughts). Types include erotomanic, grandiose, jealous, persecutory, somatic, mixed, and unspecified. |
| **Disorganized thought** | Speech may be incoherent ("word salad"), tangential, or derailed ("loose associations"). |
| **Hallucinations** | Perceptions in the absence of external stimuli (eg, seeing a light that is not actually present). Contrast with misperceptions (eg, illusions) of real external stimuli. Types include:<br>▪ Auditory—more commonly due to psychiatric illness (eg, schizophrenia) than medical illness.<br>▪ Visual—more commonly due to medical illness (eg, drug intoxication, delirium) than psychiatric illness.<br>▪ Tactile—common in alcohol withdrawal and stimulant use (eg, "cocaine crawlies," a type of delusional parasitosis).<br>▪ Olfactory—often occur as an aura of temporal lobe epilepsy (eg, burning rubber) and in brain tumors.<br>▪ Gustatory—rare, but seen in epilepsy.<br>▪ Hypna**go**gic—occurs while **go**ing to sleep. Sometimes seen in narcolepsy.<br>▪ Hypno**pomp**ic—occurs while waking from sleep ("get **pomp**ed up in the morning"). Sometimes seen in narcolepsy.<br>Contrast with illusions, which are misperceptions of real external stimuli (eg, mistaking a shadow for a black cat). |

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| **Mood disorder** | Characterized by an abnormal range of moods or internal emotional states and loss of control over them. Severity of moods causes distress and impairment in social and occupational functioning. Includes major depressive, bipolar, dysthymic, and cyclothymic disorders. Episodic superimposed psychotic features (delusions, hallucinations, disorganized speech/behavior) may be present. |

## Schizophrenia spectrum disorders

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| **Schizophrenia** | Chronic illness causing profound functional impairment. Symptom categories include:<br>▪ Positive—excessive or distorted functioning (eg, hallucinations, delusions, unusual thought processes, disorganized speech, bizarre behavior)<br>▪ Negative—diminished functioning (eg, flat or blunted affect, apathy. anhedonia, alogia, social withdrawal)<br>▪ Cognitive—reduced ability to understand or make plans, diminished working memory, inattention<br>Diagnosis requires ≥ 2 of the following active symptoms, including ≥ 1 from symptoms #1–3:<br>1. Delusions<br>2. Hallucinations, often auditory<br>3. Disorganized speech<br>4. Disorganized or catatonic behavior<br>5. Negative symptoms<br>Symptom onset ≥ 6 months prior to diagnosis; requires ≥ 1 month of active symptoms over the past 6 months. | Associated with altered dopaminergic activity, ↑ serotonergic activity, and ↓ dendritic branching. Ventriculomegaly on brain imaging. Lifetime prevalence—1.5% (males > females). Presents earlier in males (late teens to early 20s) than in females (late 20s to early 30s). ↑ suicide risk.<br>Heavy cannabis use in adolescence is associated with ↑ incidence and worsened course of psychotic, mood, and anxiety disorders.<br>Treatment: atypical antipsychotics (eg, risperidone) are first line.<br>Negative symptoms often persist after treatment, despite resolution of positive symptoms. |
| | Brief psychotic disorder—≥ 1 positive symptom(s) lasting < 1 month, usually stress-related.<br>Schizophreniform disorder—≥ 2 symptoms lasting 1–6 months. | |
| **Schizoaffective disorder** | Shares symptoms with both schizophrenia and mood disorders (major depressive or bipolar disorder). To differentiate from a mood disorder with psychotic features, patient must have > 2 weeks of psychotic symptoms without a manic or depressive episode. | |
| **Delusional disorder** | ≥ 1 delusion(s) lasting > 1 month, but without a mood disorder or other psychotic symptoms. Daily functioning, including socialization, may be impacted by the pathological, fixed belief but is otherwise unaffected. Can be shared by individuals in close relationships (folie à deux). | |
| **Schizotypal personality disorder** | Cluster A personality disorder that also falls on the schizophrenia spectrum. May include brief psychotic episodes (eg, delusions) that are less frequent and severe than in schizophrenia. | |

## Manic episode

Distinct period of abnormally and persistently elevated, expansive, or irritable mood and ↑ activity or energy lasting ≥ 1 week. Diagnosis requires hospitalization or marked functional impairment with ≥ 3 of the following (manics **DIG FAST**):

- **D**istractibility
- **I**mpulsivity/**I**ndiscretion—seeks pleasure without regard to consequences (hedonistic)
- **G**randiosity—inflated self-esteem
- **F**light of ideas—racing thoughts
- ↑ goal-directed **A**ctivity/psychomotor **A**gitation
- ↓ need for **S**leep
- **T**alkativeness or pressured speech

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| **Hypomanic episode** | Similar to a manic episode except mood disturbance is not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization. Abnormally ↑ activity or energy usually present. No psychotic features. Lasts ≥ 4 consecutive days. |
| **Bipolar disorder** | Bipolar I—≥ 1 manic episode +/– a hypomanic or depressive episode (may be separated by any length of time).<br>Bipolar II—a hypomanic and a depressive episode (no history of manic episodes).<br>Patient's mood and functioning usually normalize between episodes. Use of antidepressants can destabilize mood. High suicide risk. Treatment: mood stabilizers (eg, lithium, valproic acid, carbamazepine, lamotrigine), atypical antipsychotics.<br>**Cyclothymic disorder**—milder form of bipolar disorder fluctuating between mild depressive and hypomanic symptoms. Must last ≥ 2 years with symptoms present at least half of the time, with any remission lasting ≤ 2 months. |
| **Major depressive disorder** | Recurrent episodes lasting ≥ 2 weeks characterized by ≥ 5 of 9 diagnostic symptoms including depressed mood or anhedonia (or irritability in children). **SIG E CAPS**:<br>▪ **S**leep disturbances<br>▪ ↓ **I**nterest in pleasurable activities (anhedonia)<br>▪ **G**uilt or feelings of worthlessness<br>▪ ↓ **E**nergy<br>▪ ↓ **C**oncentration<br>▪ **A**ppetite/weight changes<br>▪ **P**sychomotor retardation or agitation<br>▪ **S**uicidal ideation<br>Screen for previous manic or hypomanic episodes to rule out bipolar disorder.<br>Treatment: CBT and SSRIs are first line; alternatives include SNRIs, mirtazapine, bupropion, electroconvulsive therapy (ECT), ketamine.<br>Responses to a significant loss (eg, bereavement, natural disaster, disability) may resemble a depressive episode. Diagnosis of MDD is made if criteria are met. |
| **MDD with psychotic features** | MDD + hallucinations or delusions. Psychotic features are typically mood congruent (eg, depressive themes of inadequacy, guilt, punishment, nihilism, disease, or death) and occur only in the context of major depressive episode (vs schizoaffective disorder). Treatment: antidepressant with atypical antipsychotic, ECT. |
| **Persistent depressive disorder** | Also called dysthymia. Often milder than MDD; ≥ 2 depressive symptoms lasting ≥ 2 years (≥ 1 year in children), with any remission lasting ≤ 2 months. |
| **MDD with seasonal pattern** | Formerly called seasonal affective disorder. Major depressive episodes occurring only during a particular season (usually winter) in ≥ 2 consecutive years and in most years across a lifetime. Atypical symptoms common. Treatment: standard MDD therapies + light therapy. |
| **Depression with atypical features** | Characterized by mood reactivity (transient improvement in response to a positive event), hypersomnia, hyperphagia, leaden paralysis (heavy feeling in arms and legs), long-standing interpersonal rejection sensitivity. Most common subtype of depression. Treatment: CBT and SSRIs are first line. MAO inhibitors (MAOIs) are effective but not first line because of their risk profile. |

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| **Peripartum mood disturbances** | Onset during pregnancy or within 4 weeks of delivery. ↑ risk with history of mood disorders. |
| **Postpartum blues** | 50–85% incidence rate. Characterized by depressed affect, tearfulness, and fatigue starting 2–3 days after delivery. Usually resolves within 2 weeks. Treatment: supportive. Follow up to assess for possible MDD with peripartum onset. |
| **MDD with peripartum onset** | 10–15% incidence rate. Formerly called postpartum depression. Meets MDD criteria with onset no later than 1 year after delivery. Treatment: CBT and SSRIs are first line. |
| **Postpartum psychosis** | 0.1–0.2% incidence rate. Characterized by mood-congruent delusions, hallucinations, and thoughts of harming the baby or self. Risk factors include first pregnancy, family history, bipolar disorder, psychotic disorder, recent medication change. Treatment: hospitalization and initiation of atypical antipsychotic; if insufficient, ECT may be used. |

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| **Electroconvulsive therapy** | Rapid-acting method to treat refractory depression, depression with psychotic symptoms, catatonia, and acute suicidality. Induces tonic-clonic seizure under anesthesia and neuromuscular blockade. Adverse effects include disorientation, headache, partial anterograde/retrograde amnesia usually resolving in 6 months. No absolute contraindications. Safe in pregnant and elderly individuals. |

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| **Risk factors for suicide completion** | **S**ex (male)<br>**A**ge (young adult or elderly)<br>**D**epression<br>**P**revious attempt (highest risk factor)<br>**E**thanol or drug use<br>**R**ational thinking loss (psychosis)<br>**S**ickness (medical illness)<br>**O**rganized plan<br>**N**o spouse or other social support<br>**S**tated future intent | **SAD PERSONS** are more likely to complete suicide.<br>Most common method in US is firearms; access to guns ↑ risk of suicide completion.<br>Women try more often; men complete more often.<br>Other risk factors include recent psychiatric hospitalization and family history of completed suicide.<br>Protective factors include effective care for comorbidities; medical, familial, or community connectedness; cultural/religious beliefs encouraging self-preservation; and strong problem-solving skills. |

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| **Anxiety disorders** | Inappropriate experiences of fear/worry and their physical manifestations incongruent with the magnitude of the stressors. Symptoms are not attributable to another psychiatric disorder, medical condition (eg, hyperthyroidism), or substance use. Includes panic disorder, phobias, generalized anxiety disorder, and selective mutism. |

**Panic disorder**

Recurrent panic attacks involving intense fear and discomfort +/– a known trigger. Attacks typically peak in 10 minutes with ≥ 4 of the following: palpitations, paresthesias, depersonalization or derealization, abdominal pain, nausea, intense fear of dying, intense fear of losing control, lightheadedness, chest pain, chills, choking, sweating, shaking, shortness of breath. Strong genetic component. ↑ risk of suicide.

Diagnosis requires attack followed by ≥ 1 month of ≥ 1 of the following:
- Persistent concern of additional attacks
- Worrying about consequences of attack
- Behavioral change related to attacks

Symptoms are systemic manifestations of fear.
Treatment: CBT, SSRIs, and venlafaxine are first line. Benzodiazepines occasionally used in acute setting.

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**Phobias**

Severe, persistent (≥ 6 months) fear or anxiety due to presence or anticipation of a specific object or situation. Person often recognizes fear is excessive. Treatment: CBT with exposure therapy.

**Social anxiety disorder**—exaggerated fear of embarrassment in social situations (eg, public speaking, using public restrooms). Treatment: CBT, SSRIs, venlafaxine. For performance type (eg, anxiety restricted to public speaking), use β-blockers or benzodiazepines as needed.

**Agoraphobia**—irrational fear/anxiety while facing or anticipating ≥ 2 specific situations (eg, open/closed spaces, lines, crowds, public transport). If severe, patients may refuse to leave their homes. Associated with panic disorder. Treatment: CBT, SSRIs.

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**Generalized anxiety disorder**

Excessive anxiety and worry about different aspects of daily life (eg, work, school, children) for most days of ≥ 6 months. Associated with ≥ 3 of the following for adults (≥ 1 for kids): restlessness, irritability, sleep disturbance, fatigue, muscle tension, difficulty concentrating. Treatment: CBT, SSRIs, SNRIs are first line. Buspirone, TCAs, benzodiazepines are second line.

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**Obsessive-compulsive disorders**

Obsessions (recurring intrusive thoughts, feelings, or sensations) that cause severe distress, relieved in part by compulsions (performance of repetitive, often time-consuming actions). Ego-dystonic: behavior inconsistent with one's beliefs and attitudes (vs obsessive-compulsive personality disorder, ego-syntonic). Associated with Tourette syndrome. Treatment: CBT and SSRIs; clomipramine and venlafaxine are second line.

**Body dysmorphic disorder**—preoccupation with minor or imagined defects in appearance. Causes significant emotional distress and repetitive appearance-related behaviors (eg, mirror checking, excessive grooming). Common in eating disorders. Treatment: CBT.

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**Trichotillomania**

Compulsively pulling out one's hair. Causes significant distress and persists despite attempts to stop. Presents with areas of thinning hair or baldness on any area of the body, most commonly the scalp A. Remaining hair shafts are of different lengths (vs alopecia). Incidence highest in childhood but spans all ages. Treatment: psychotherapy.

## Trauma and stress-related disorders

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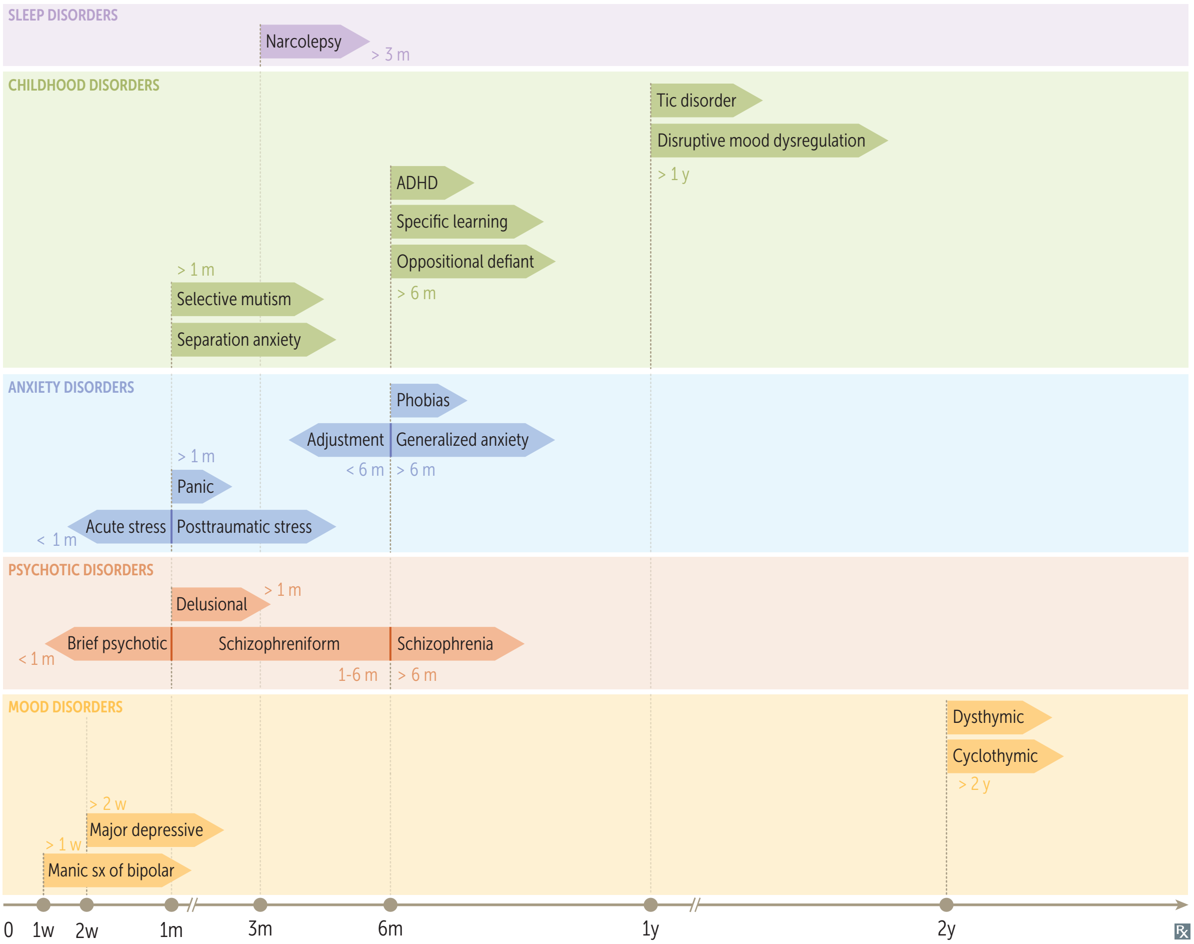
| **Adjustment disorder** | Emotional or behavioral symptoms (eg, anxiety, outbursts) that occur within 3 months of an identifiable psychosocial stressor (eg, divorce, illness) lasting < 6 months once the stressor has ended. Symptoms do not meet criteria for another psychiatric illness. If symptoms persist > 6 months after stressor ends, reevaluate for other explanations (eg, MDD, GAD). Treatment: CBT is first line; antidepressants and anxiolytics may be considered. |
| **Post-traumatic stress disorder** | Experiencing, or discovering that a loved one has experienced, a life-threatening situation (eg, serious injury, rape, witnessing death) → persistent **H**yperarousal, **A**voidance of associated stimuli, intrusive **R**e-experiencing of the event (eg, nightmares, flashbacks), changes in cognition or mood (eg, fear, horror, **D**istress) (having PTSD is **HARD**). Disturbance lasts > 1 month with significant distress or impaired functioning. Treatment: CBT, SSRIs, and venlafaxine are first line. Prazosin can reduce nightmares.<br>Acute stress disorder—lasts between 3 days and 1 month. Treatment: CBT; pharmacotherapy is usually not indicated. |

## Diagnostic criteria by symptom duration



## Personality

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| **Personality trait** | An enduring, repetitive pattern of perceiving, relating to, and thinking about the environment and oneself. | |
| **Personality disorder** | Inflexible, maladaptive, and rigidly pervasive pattern of behavior causing subjective distress and/or impaired functioning; person is usually not aware of problem (ego-syntonic). Usually presents by early adulthood.<br>Three clusters: A, B, C; remember as **weird**, **wild**, and **worried**, respectively, based on symptoms. | |

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| **Cluster A personality disorders** | Odd or eccentric; inability to develop meaningful social relationships. No psychosis; genetic association with schizophrenia. | Cluster A: accusatory, aloof, awkward. "**Weird**." |
| **Paranoid** | Pervasive distrust (accusatory), suspiciousness, hypervigilance, and a profoundly cynical view of the world. | |
| **Schizoid** | Prefers social withdrawal and solitary activities (vs avoidant), limited emotional expression, indifferent to others' opinions (Aloof). | |
| **Schizotypal** | Eccentric appearance, odd beliefs or magical thinking, interpersonal Awkwardness. | Included on the schizophrenia spectrum.<br>Pronounce schizo-**type**-al: odd-**type** thoughts. |

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| **Cluster B personality disorders** | Dramatic, emotional, or erratic; genetic association with mood disorders and substance use. | Cluster B: bad, borderline, flamboyant, must be the best. "**Wild**." |
| **Antisocial** | Disregard for the rights of others with lack of remorse. Involves criminality, impulsivity, hostility, and manipulation. Males > females. Must be ≥ 18 years old with evidence of conduct disorder onset before age 15. Diagnosis is conduct disorder if < 18 years old. | Antisocial = sociopath.<br>Bad. |
| **Borderline** | Unstable mood and interpersonal relationships, fear of abandonment, impulsivity, self-mutilation, suicidality, sense of emotional emptiness. Females > males. Splitting is a major defense mechanism. | Treatment: dialectical behavior therapy.<br>Borderline. |
| **Histrionic** | Attention-seeking, dramatic speech and emotional expression, shallow and labile emotions, sexually provocative. May use physical appearance to draw attention. | Flamboyant. |
| **Narcissistic** | Grandiosity, sense of entitlement; lacks empathy and requires excessive admiration; often demands the "best" and reacts to criticism with rage and/or defensiveness. Fragile self-esteem. Often envious of others. | Must be the best. |

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| **Cluster C personality disorders** | Anxious or fearful; genetic association with anxiety disorders. | Cluster **C**: **c**owardly, obsessive-**c**ompulsive, **c**lingy. "**Worried**." |
| **Avoidant** | Hypersensitive to rejection and criticism, socially inhibited, timid, feelings of inadequacy, desires relationships with others (vs schizoid). | **C**owardly. |
| **Obsessive-compulsive** | Preoccupation with order, perfectionism, and control; ego-syntonic: behavior consistent with one's own beliefs and attitudes (vs OCD). | |
| **Dependent** | Excessive need for support, low self-confidence. Patients often get stuck in abusive relationships. | Submissive and **c**lingy. |

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| **Malingering** | Symptoms are intentional, motivation is intentional. Patient consciously fakes, profoundly exaggerates, or claims to have a disorder in order to attain a specific 2° (external) gain (eg, avoiding work, obtaining compensation). Poor compliance with treatment or follow-up of diagnostic tests. Complaints cease after gain (vs factitious disorder). |

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| **Factitious disorders** | Symptoms are intentional, motivation is unconscious. Patient consciously creates physical and/or psychological symptoms in order to assume "sick role" and to get medical attention and sympathy (1° [internal] gain). |
| **Factitious disorder imposed on self** | Formerly called Munchausen syndrome. Chronic factitious disorder with predominantly physical signs and symptoms. Characterized by a history of multiple hospital admissions and willingness to undergo invasive procedures. More common in women and healthcare workers. |
| **Factitious disorder imposed on another** | Formerly called Munchausen syndrome by proxy. Illness in a child or elderly patient is caused or fabricated by the caregiver. Motivation is to assume a sick role by proxy. Form of child/elder abuse. |

| | |
|---|---|
| **Somatic symptom and related disorders** | Symptoms are unconscious, motivation is unconscious. Category of disorders characterized by physical symptoms causing significant distress and impairment. Symptoms not intentionally produced or feigned. |
| **Somatic symptom disorder** | ≥ 1 bodily complaints (eg, abdominal pain, fatigue) lasting months to years. Associated with excessive, persistent thoughts and anxiety about symptoms. May co-occur with medical illness. Treatment: regular office visits with the same physician in combination with psychotherapy. |
| **Conversion disorder** | Also called functional neurologic symptom disorder. Unexplained loss of sensory or motor function (eg, paralysis, blindness, mutism), often following an acute stressor; patient may be aware of but indifferent toward symptoms ("la belle indifférence"); more common in females, adolescents, and young adults. |
| **Illness anxiety disorder** | Preoccupation with acquiring or having a serious illness, often despite medical evaluation and reassurance; minimal to no somatic symptoms. |

**Malingering vs factitious disorder vs somatic symptom disorders**

| | Malingering | Factitious disorder | Somatic symptom disorders |
|---|---|---|---|
| SYMPTOMS | Intentional | Intentional | Unconscious |
| MOTIVATION | Intentional | Unconscious | Unconscious |

| | |
|---|---|
| **Eating disorders** | Most common in young women. |
| **Anorexia nervosa** | Intense fear of weight gain, overvaluation of thinness, and body image distortion leading to calorie restriction and severe weight loss resulting in inappropriately low body weight (BMI < 18.5 kg/$m^2$ for adults). May present with hypothyroidism, amenorrhea, osteoporosis, lanugo.<br>Binge-eating/purging type—recurring purging behaviors (eg, laxative or diuretic abuse, self-induced vomiting) or binge eating over the last 3 months.<br>Restricting type—primary disordered behaviors include dieting, fasting, and/or over-exercising. No recurring purging behaviors or binge eating over the last 3 months.<br>Refeeding syndrome—often occurs in significantly malnourished patients with sudden ↑ calorie intake → ↑ insulin → ↓ $PO_4^{3-}$, ↓ $K^+$, ↓ $Mg^{2+}$ → cardiac complications, rhabdomyolysis, seizures.<br>Treatment: nutritional rehabilitation, psychotherapy, olanzapine. |
| **Bulimia nervosa** | Recurring episodes of binge eating with compensatory purging behaviors at least weekly over the last 3 months. BMI often normal or slightly overweight (vs anorexia). Associated with parotid gland hypertrophy (may see ↑ serum amylase), enamel erosion, Mallory-Weiss syndrome, electrolyte disturbances (eg, ↓ $K^+$, ↓ $Cl^-$), metabolic alkalosis, dorsal hand calluses from induced vomiting (Russell sign).<br>Treatment: psychotherapy, nutritional rehabilitation, antidepressants (eg, SSRIs). Bupropion is contraindicated due to seizure risk. |
| **Binge-eating disorder** | Recurring episodes of binge eating without purging behaviors at least weekly over the last 3 months. ↑ diabetes risk. Most common eating disorder in adults.<br>Treatment: psychotherapy (first line); SSRIs; lisdexamfetamine. |
| **Pica** | Recurring episodes of eating non-food substances (eg, ice, dirt, hair, paint chips) over ≥ 1 month that are not culturally or developmentally recognized as normal. May provide temporary emotional relief. Common in children and during pregnancy. Associated with malnutrition, iron deficiency anemia, developmental disabilities, emotional trauma.<br>Treatment: psychotherapy and nutritional rehabilitation (first line); SSRIs (second line). |

| | |
|---|---|
| **Gender dysphoria** | Significant incongruence between one's experienced gender and the gender assigned at birth, lasting > 6 months and leading to persistent distress. Individuals may self-identify as another gender, pursue gender-affirming surgery, and/or live as another gender. Gender nonconformity itself is not a mental disorder. Gender identity develops at age ~3 years.<br>**Transgender**—desiring and often making lifestyle changes to live as a different gender. Medical interventions (eg, hormone therapy, gender-affirming surgery) may be utilized during the transition to enable the individual's appearance to match their gender identity. |

| | |
|---|---|
| **Sexual dysfunction** | Includes sexual desire disorders (hypoactive sexual desire or sexual aversion), sexual arousal disorders (erectile dysfunction), orgasmic disorders (anorgasmia, premature ejaculation), sexual pain disorders (dyspareunia, vaginismus).<br>Differential diagnosis includes (**PENIS**):<br>▪ **P**sychological (if nighttime erections still occur)<br>▪ **E**ndocrine (eg, diabetes, low testosterone)<br>▪ **N**eurogenic (eg, postoperative, spinal cord injury)<br>▪ **I**nsufficient blood flow (eg, atherosclerosis)<br>▪ **S**ubstances (eg, antihypertensives, antidepressants, ethanol) |

| | |
|---|---|
| **Sleep terror disorder** | Periods of inconsolable terror with screaming in the middle of the night. Most common in children. Occurs during slow-wave/deep (stage N3) non-REM sleep with no memory of the arousal episode, as opposed to nightmares that occur during **REM** sleep (**rem**embering a scary dream). Triggers include emotional stress, fever, and lack of sleep. Usually self limited. |
| **Enuresis** | Nighttime urinary incontinence ≥ 2 times/week for ≥ 3 months in person > 5 years old. First-line treatment: behavioral modification (eg, scheduled voids, nighttime fluid restriction) and positive reinforcement. For refractory cases: bedwetting alarm, oral desmopressin (ADH analog; preferred over imipramine due to fewer side effects). |
| **Narcolepsy** | Excessive daytime sleepiness (despite awakening well-rested) with recurrent episodes of rapid-onset, overwhelming sleepiness ≥ 3 times/week for the last 3 months. Due to ↓ orexin (hypocretin) production in lateral hypothalamus and dysregulated sleep-wake cycles. Associated with:<br>▪ Hypna**go**gic (just before **go**ing to sleep) or hypno**pomp**ic (just before awakening; get **pomp**ed up in the morning) hallucinations.<br>▪ Nocturnal and narcoleptic sleep episodes that start with REM sleep (sleep paralysis).<br>▪ Cataplexy (loss of all muscle tone following strong emotional stimulus, such as laughter).<br>Treatment: good sleep hygiene (scheduled naps, regular sleep schedule), daytime stimulants (eg, amphetamines, modafinil) and/or nighttime sodium oxybate (GHB). |
| **Substance use disorder** | Maladaptive pattern of substance use involving ≥ 2 of the following in the past year:<br>▪ Tolerance<br>▪ Withdrawal<br>▪ Intense, distracting cravings<br>▪ Using more, or longer, than intended<br>▪ Persistent desire but inability to cut down<br>▪ Time-consuming substance acquisition, use, or recovery<br>▪ Impaired functioning at work, school, or home<br>▪ Social or interpersonal conflicts<br>▪ Reduced recreational activities<br>▪ > 1 episode of use involving danger (eg, unsafe sex, driving while impaired)<br>▪ Continued use despite awareness of harm |
| **Gambling disorder** | Persistent, recurrent, problematic gambling. May include preoccupation with gambling, compulsion to increase size of bet, unsuccessful attempts to decrease gambling, gambling to escape stressors, attempting to recoup losses with more gambling, lying to family or therapists to conceal extent. Treatment: psychotherapy. |

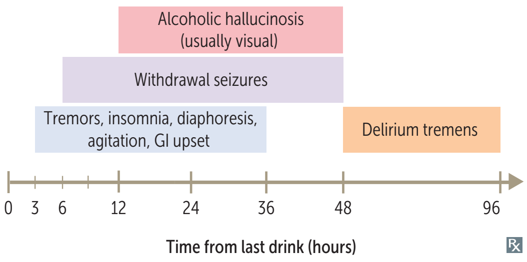
### Transtheoretical model of change

| STAGE | FEATURES | MOTIVATIONAL STRATEGIES |
|---|---|---|
| **Precontemplation** | Denies problem and its consequences. | Encourage introspection. Use patient's personal priorities in explaining risks. Affirm your availability to the patient. |
| **Contemplation** | Acknowledges problem but is ambivalent or unwilling to change. | Discuss pros of changing and cons of maintaining current behavior. Suggest means to support behavior changes. |
| **Preparation/ determination** | Committed to and planning for behavior change. | Encourage initial changes, promote expectations for positive results, provide resources to assist in planning. |
| **Action/willpower** | Executes a plan and demonstrates a change in behavior. | Assist with strategies for self-efficacy, contingency management, and coping with situations that trigger old behaviors. |
| **Maintenance** | New behaviors become sustained, integrate into personal identity and lifestyle. | Reinforce developing habits. Evaluate and mitigate relapse risk. Praise progress. |
| **Relapse** | Regression to prior behavior (does not always occur). | Varies based on degree of regression. Encourage return to changes. Provide reassurance that change remains possible. |

## Psychiatric emergencies

| | CAUSE | MANIFESTATION | TREATMENT |
|---|---|---|---|
| **Serotonin syndrome** | Any drug that ↑ 5-HT.<br>Psychiatric drugs: MAOIs, SSRIs, SNRIs, TCAs, vilazodone, vortioxetine, buspirone<br>Nonpsychiatric drugs: tramadol, ondansetron, triptans, linezolid, MDMA, dextromethorphan, meperidine, St. John's wort | **3 A**'s: ↑ **a**ctivity (neuromuscular; eg, clonus, hyperreflexia, hypertonia, tremor, seizure), **a**utonomic instability (eg, hyperthermia, diaphoresis, diarrhea), **al**tered mental status | Cyproheptadine ($5\text{-}HT_2$ receptor antagonist)<br>Prevention: avoid simultaneous serotonergic drugs, and allow a washout period between them |
| **Hypertensive crisis** | Eating tyramine-rich foods (eg, aged cheeses, cured meats, wine, chocolate) while taking MAOIs | Hypertensive crisis (tyramine displaces other neurotransmitters [eg, NE] in the synaptic cleft → ↑ sympathetic stimulation) | Phentolamine |
| **Neuroleptic malignant syndrome** | Antipsychotics (typical > atypical) + genetic predisposition | **M**alignant **FEVER**: **M**yoglobinuria, **F**ever, **E**ncephalopathy, **V**itals unstable, ↑ **E**nzymes (eg, CK), muscle **R**igidity ("lead pipe") | Dantrolene, dopaminergics (eg, bromocriptine, amantadine), benzodiazepines; discontinue causative agent |
| **Delirium tremens** | Alcohol withdrawal; occurs 2–4 days after last drink<br>Classically seen in hospital setting when inpatient cannot drink | Altered mental status, hallucinations, autonomic hyperactivity, anxiety, seizures, tremors, psychomotor agitation, insomnia, nausea | Longer-acting benzodiazepines |
| **Acute dystonia** | Typical antipsychotics, anticonvulsants (eg, carbamazepine), metoclopramide | Sudden onset of muscle spasms, stiffness, and/or oculogyric crisis occurring hours to days after medication use; can lead to laryngospasm requiring intubation | Benztropine or diphenhydramine |
| **Lithium toxicity** | ↑ lithium dosage, ↓ renal elimination (eg, acute kidney injury), medications affecting clearance (eg, ACE inhibitors, thiazide diuretics, NSAIDs). Narrow therapeutic window. | Nausea, vomiting, slurred speech, hyperreflexia, seizures, ataxia, nephrogenic diabetes insipidus | Discontinue lithium, hydrate aggressively with isotonic sodium chloride, consider hemodialysis |
| **Tricyclic antidepressant toxicity** | TCA overdose | Respiratory depression, hyperpyrexia, prolonged QT<br>**Tricyclic**'s: **c**onvulsions, **c**oma, **c**ardiotoxicity (arrhythmia due to $Na^+$ channel inhibition) | Supportive treatment, monitor ECG, $NaHCO_3$ (prevents arrhythmia), activated charcoal |

## Psychoactive drug intoxication and withdrawal

| DRUG | INTOXICATION | WITHDRAWAL |
|---|---|---|
| **Depressants** | | |
| | Nonspecific: mood elevation, ↓ anxiety, sedation, behavioral disinhibition, respiratory depression. | Nonspecific: anxiety, tremor, seizures, insomnia. |
| **Alcohol** | Emotional lability, slurred speech, ataxia, coma, blackouts. Serum γ-glutamyltransferase (GGT)—sensitive indicator of alcohol use. **AST** value is **2**× **ALT** value ("To**AST 2 AL**cohol"). Treatment: supportive (eg, fluids, antiemetics). |   Treatment: longer-acting benzodiazepines. |
| **Barbiturates** | Low safety margin, marked respiratory depression. Treatment: symptom management (eg, assist respiration, ↑ BP). | Delirium, life-threatening cardiovascular collapse. |
| **Benzodiazepines** | Greater safety margin. Ataxia, minor respiratory depression. Treatment: flumazenil (benzodiazepine receptor antagonist, but rarely used as it can precipitate seizures). | Seizures, sleep disturbance, depression. |
| **Opioids** | Euphoria, respiratory and CNS depression, ↓ gag reflex, pupillary constriction (pinpoint pupils), seizures, ↓ GI motility. Most common cause of drug overdose death. Treatment: naloxone. | Sweating, dilated pupils, piloerection ("cold turkey"), rhinorrhea, lacrimation, yawning, nausea, stomach cramps, diarrhea ("flu-like" symptoms). Treatment: symptom management, methadone, buprenorphine. |
| **Inhalants** | Disinhibition, euphoria, slurred speech, disturbed gait, disorientation, drowsiness. Effects often have rapid onset and resolution. Perinasal/perioral rash with repeated use. | Irritability, dysphoria, sleep disturbance, headache. |
| **Stimulants** | | |
| | Nonspecific: mood elevation, ↓ appetite, psychomotor agitation, insomnia, cardiac arrhythmias, tachycardia, anxiety. | Nonspecific: post-use "crash," including depression, lethargy, ↑ appetite, sleep disturbance, vivid nightmares. |
| **Amphetamines** | Euphoria, grandiosity, pupillary dilation, prolonged wakefulness, hyperalertness, hypertension, paranoia, fever, fractured teeth. Skin excoriations with methamphetamine use. Severe: cardiac arrest, seizures. Treatment: benzodiazepines for agitation and seizures. | |
| **Caffeine** | Palpitation, agitation, tremor, insomnia. | Headache, difficulty concentrating, flu-like symptoms. |

**Psychoactive drug intoxication and withdrawal *(continued)***

| DRUG | INTOXICATION | WITHDRAWAL |
|---|---|---|
| **Cocaine** | Impaired judgment, pupillary dilation, diaphoresis, hallucinations (including tactile), paranoia, angina, sudden cardiac death. Chronic use may lead to perforated nasal septum due to vasoconstriction and resulting ischemic necrosis. Treatment: benzodiazepines; use of β-blockers or mixed α-/β-blockers (eg, labetalol) for hypertension and tachycardia is controversial as first-line therapy. | Restlessness, hunger, severe depression, sleep disturbance. |
| **Nicotine** | Restlessness. | Irritability, anxiety, restlessness, ↓ concentration, ↑ appetite/weight. Treatment: nicotine patch, gum, or lozenges; bupropion/varenicline. |
| Hallucinogens | | |
| **Lysergic acid diethylamide** | Perceptual distortion (visual, auditory), depersonalization, anxiety, paranoia, psychosis, flashbacks (usually nondisturbing), mydriasis. | |
| **Cannabis/ cannabinoids** | Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired judgment, social withdrawal, ↑ appetite, dry mouth, conjunctival injection, hallucinations. | Irritability, anxiety, depression, insomnia, restlessness, ↓ appetite. |
| **MDMA** | Also known as ecstasy. Euphoria, hallucinations, disinhibition, hyperactivity, ↑ thirst, bruxism, distorted sensory and time perception, mydriasis. Life-threatening effects include hypertension, tachycardia, hyperthermia, hyponatremia, serotonin syndrome. | Depression, fatigue, change in appetite, difficulty concentrating, anxiety. |
| **Phencyclidine** | Violence, nystagmus, impulsivity, psychomotor agitation, miosis, tachycardia, hypertension, analgesia, psychosis, delirium, seizures. | |

| | |
|---|---|
| **Alcohol use disorder** | Diagnosed using criteria for substance use disorder.<br>Complications: vitamin $B_1$ (thiamine) deficiency, alcoholic cirrhosis, hepatitis, pancreatitis, peripheral neuropathy, testicular atrophy.<br>Treatment: naltrexone (reduces cravings), acamprosate, disulfiram (to condition the patient to abstain from alcohol use). Support groups such as Alcoholics Anonymous are helpful in sustaining abstinence and supporting patient and family. |
| **Wernicke-Korsakoff syndrome** | Results from vitamin $B_1$ deficiency. Symptoms can be precipitated by administering dextrose before vitamin $B_1$. Triad of confusion, ophthalmoplegia, ataxia (Wernicke encephalopathy). May progress to irreversible memory loss, confabulation, personality change (Korsakoff syndrome).<br>Treatment: IV vitamin $B_1$ (before dextrose). |

## ▸ PSYCHIATRY—PHARMACOLOGY

### Psychotherapy

| | |
|---|---|
| **Behavioral therapy** | Teaches patients how to identify and change maladaptive behaviors or reactions to stimuli (eg, systematic desensitization for specific phobia). |
| **Cognitive behavioral therapy** | Teaches patients to recognize distortions in their thought processes, develop constructive coping skills, and ↓ maladaptive coping behaviors → greater emotional control and tolerance of distress (eg, recognizing triggers for alcohol consumption). |
| **Dialectical behavioral therapy** | Designed for use in borderline personality disorder, but can be used in other psychiatric conditions as well (eg, depression). |
| **Interpersonal therapy** | Focused on improving interpersonal relationships and communication skills. |
| **Motivational interviewing** | Enhances intrinsic motivation to change by exploring and resolving ambivalence. Used in substance use disorder and weight loss. |
| **Supportive therapy** | Utilizes empathy to help individuals during a time of hardship to maintain optimism or hope. |

### Preferred medications for selected psychiatric conditions

| PSYCHIATRIC CONDITION | PREFERRED DRUGS |
|---|---|
| ADHD | Stimulants (methylphenidate, amphetamines) |
| Alcohol withdrawal | Benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam) |
| Bipolar disorder | **C**arbamazepine, **a**typical antipsychotics, **l**ithium, **l**amotrigine, **v**alproate. **C**haracter **a** **l**ittle **l**ess **v**ariable |
| Bulimia nervosa | SSRIs |
| Depression | SSRIs |
| Generalized anxiety disorder | SSRIs, SNRIs |
| Obsessive-compulsive disorder | SSRIs, venlafaxine, clomipramine |
| Panic disorder | SSRIs, venlafaxine, benzodiazepines |
| PTSD | SSRIs, venlafaxine, prazosin (for nightmares) |
| Schizophrenia | Atypical antipsychotics |
| Social anxiety disorder | SSRIs, venlafaxine<br>Performance only: β-blockers, benzodiazepines |
| Tourette syndrome | Antipsychotics (eg, fluphenazine, risperidone), tetrabenazine |

### Central nervous system stimulants

Methylphenidate, dextroamphetamine, methamphetamine, lisdexamfetamine.

| | |
|---|---|
| MECHANISM | ↑ catecholamines in the synaptic cleft, especially norepinephrine and dopamine. |
| CLINICAL USE | ADHD, narcolepsy, binge-eating disorder. |
| ADVERSE EFFECTS | Nervousness, agitation, anxiety, insomnia, anorexia, tachycardia, hypertension, weight loss, tics, bruxism. |

| | |
|---|---|
| **Antipsychotics** | Typical (1st-generation) antipsychotics—haloperidol, pimozide, trifluoper**azine**, fluphen**azine**, thiorid**azine**, chlorprom**azine**.<br>Atypical (2nd-generation) antipsychotics—aripiprazole, asen**apine**, cloz**apine**, olanz**apine**, queti**apine**, iloper**idone**, paliper**idone**, risper**idone**, luras**idone**, zipras**idone**. |
| MECHANISM | Block dopamine $D_2$ receptor (↑ cAMP). Atypical antipsychotics also block serotonin 5-$HT_2$ receptor. Aripiprazole is a $D_2$ partial agonist. |
| CLINICAL USE | Schizophrenia (typical antipsychotics primarily treat positive symptoms; atypical antipsychotics treat both positive and negative symptoms), disorders with concomitant psychosis (eg, bipolar disorder), Tourette syndrome, OCD, Huntington disease. Clozapine is used for treatment-resistant psychotic disorders or those with persistent suicidality. |
| ADVERSE EFFECTS | Anti**h**istaminic (sedation), anti-$\alpha_1$-adrenergic (orthostatic hypotension), anti**m**uscarinic (dry mouth, constipation) (anti-**HAM**). Use with caution in dementia.<br>Metabolic: weight gain, hyperglycemia, dyslipidemia. Highest risk with cl**o**zapine and **o**lanzapine (**o**besity).<br>Endocrine: hyperprolactinemia → galactorrhea, oligomenorrhea, gynecomastia.<br>Cardiac: QT prolongation.<br>Neurologic: neuroleptic malignant syndrome.<br>Ophthalmologic: **chlor**promazine—**cor**neal deposits; **t**hioridazine—re**t**inal deposits.<br>**Cloz**apine—agranulocytosis (monitor WBCs **cloz**ely), seizures (dose related), myocarditis.<br>Extrapyramidal symptoms—**ADAPT**:<br>▪ Hours to days: **A**cute **D**ystonia (muscle spasm, stiffness, oculogyric crisis). Treatment: benztropine, diphenhydramine.<br>▪ Days to months:<br>  ▪ **A**kathisia (restlessness). Treatment: β-blockers, benztropine, benzodiazepines.<br>  ▪ **P**arkinsonism (bradykinesia). Treatment: benztropine, amantadine.<br>▪ Months to years: **T**ardive dyskinesia (chorea, especially orofacial). Treatment: benzodiazepines, botulinum toxin injections, valbenazine, deutetrabenazine. |
| NOTES | Lipid soluble → stored in body fat → slow to be removed from body.<br>Typical antipsychotics have greater affinity for $D_2$ receptor than atypical antipsychotics → ↑ risk for hyperprolactinemia, extrapyramidal symptoms, neuroleptic malignant syndrome.<br>**High**-potency typical antipsychotics: **hal**operidol, **tri**fluoperazine, **pi**mozide, **fl**uphenazine (**Hal tri**es **pie** to **fl**y **high**)—more neurologic side effects (eg, extrapyramidal symptoms).<br>**Low**-potency typical antipsychotics: **ch**lorpromazine, **thi**oridazine (**ch**eating **thi**eves are **low**)—more antihistaminic, anti-$\alpha_1$-adrenergic, antimuscarinic effects. |

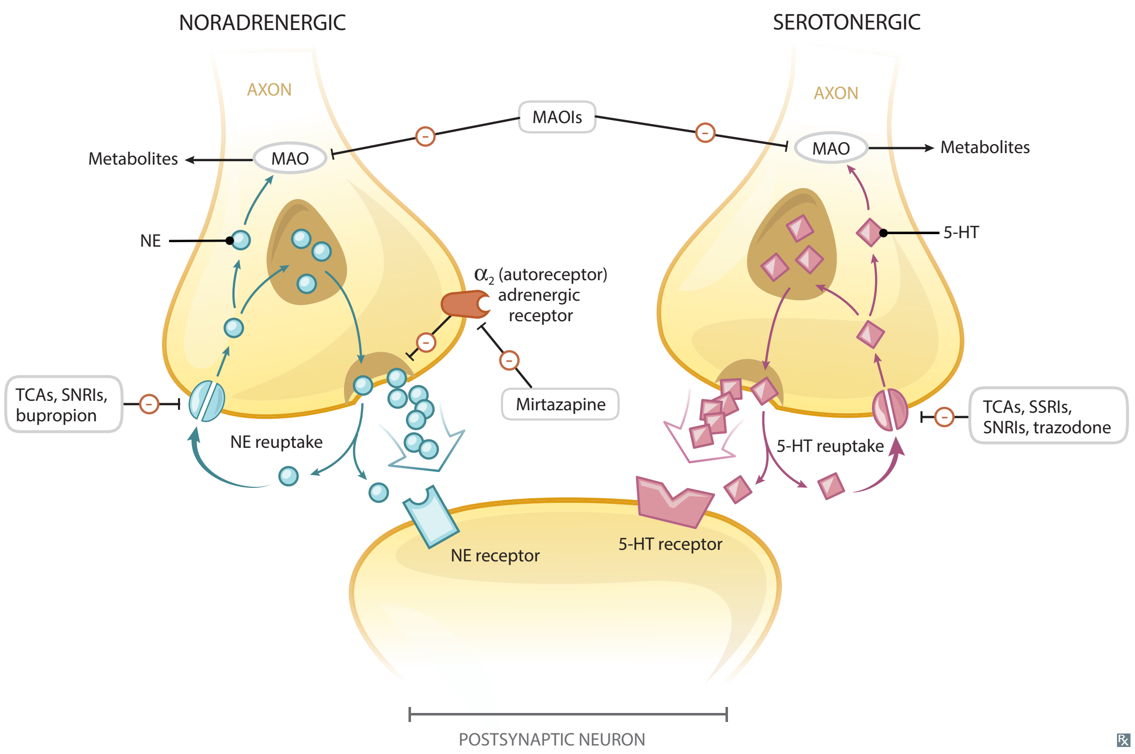
## Lithium

| | | |
|---|---|---|
| MECHANISM | Not established; possibly related to inhibition of phosphoinositol cascade. | LiTHIUM:<br>Low Thyroid (hypothyroidism)<br>Heart (Ebstein anomaly)<br>Insipidus (nephrogenic diabetes insipidus)<br>Unwanted Movements (tremor) |
| CLINICAL USE | Mood stabilizer for bipolar disorder; treats acute manic episodes and prevents relapse. | |
| ADVERSE EFFECTS | Tremor, hypothyroidism, hyperthyroidism, polyuria (causes nephrogenic diabetes insipidus), teratogenesis (causes Ebstein anomaly). Narrow therapeutic window requires close monitoring of serum levels. Almost exclusively excreted by kidneys; most is reabsorbed at PCT via $Na^+$ channels. Thiazides, NSAIDs, and other drugs affecting clearance are implicated in lithium toxicity. | |

## Buspirone

| | | |
|---|---|---|
| MECHANISM | Partial $5\text{-}HT_{1A}$ receptor agonist. | I get **anxious** if the **bus** doesn't arrive at **one**, so I take **buspirone**. |
| CLINICAL USE | Generalized **anxiety** disorder. Does not cause sedation, addiction, or tolerance. Begins to take effect after 1–2 weeks. Does not interact with alcohol (vs barbiturates, benzodiazepines). | |

## Antidepressants



| **Selective serotonin reuptake inhibitors** | Fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram, citalopram. | |
|---|---|---|
| MECHANISM | Inhibit 5-HT reuptake. | It normally takes 4–8 weeks for antidepressants to show appreciable effect. |
| CLINICAL USE | Depression, generalized anxiety disorder, panic disorder, OCD, bulimia, binge-eating disorder, social anxiety disorder, PTSD, premature ejaculation, premenstrual dysphoric disorder. | |
| ADVERSE EFFECTS | Fewer than TCAs. Serotonin syndrome, GI distress, SIADH, sexual dysfunction (anorgasmia, ↓ libido), mania precipitation if underlying bipolar disorder. | |

| **Serotonin-norepinephrine reuptake inhibitors** | Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran, milnacipran. |
|---|---|
| MECHANISM | Inhibit 5-HT and NE reuptake. |
| CLINICAL USE | Depression, generalized anxiety disorder, diabetic neuropathy. Venlafaxine is also indicated for social anxiety disorder, panic disorder, PTSD, OCD. Duloxetine and milnacipran are also indicated for fibromyalgia. |
| ADVERSE EFFECTS | ↑ BP, stimulant effects, sedation, nausea. |

| **Tricyclic antidepressants** | Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin, amoxapine. |
|---|---|
| MECHANISM | TCAs inhibit 5-HT and NE reuptake. |
| CLINICAL USE | MDD, peripheral neuropathy, chronic neuropathic pain, migraine prophylaxis, OCD (clomipramine), nocturnal enuresis (imipramine). |
| ADVERSE EFFECTS | Sedation, $\alpha_1$-blocking effects including postural hypotension, and atropine-like (anticholinergic) side effects (tachycardia, urinary retention, dry mouth). 3° TCAs (**a**mitriptyline) have more **a**nticholinergic effects than 2° TCAs (nortriptyline). Can prolong QT interval.<br>**Tri-CyCliC**'s: **C**onvulsions, **C**oma, **C**ardiotoxicity (arrhythmia due to $Na^+$ channel inhibition); also respiratory depression, hyperpyrexia. Confusion and hallucinations are more common in the elderly due to anticholinergic side effects (2° amines [eg, nortriptyline] better tolerated). Treatment: $NaHCO_3$ to prevent arrhythmia. |

| **Monoamine oxidase inhibitors** | **T**ranylcypromine, **p**henelzine, **i**socarboxazid, **s**elegiline (selective **MAO**-B inhibitor). (**MAO** **t**akes **p**ride **i**n **S**hanghai). |
|---|---|
| MECHANISM | Nonselective MAO inhibition → ↑ levels of amine neurotransmitters (norepinephrine, 5-HT, dopamine). |
| CLINICAL USE | Atypical depression, anxiety. Parkinson disease (selegiline). |
| ADVERSE EFFECTS | CNS stimulation; hypertensive crisis, most notably with ingestion of tyramine. Contraindicated with SSRIs, TCAs, St. John's wort, meperidine, dextromethorphan, pseudoephedrine, linezolid (to avoid precipitating serotonin syndrome).<br>Wait 2 weeks after stopping MAOIs before starting serotonergic drugs or stopping dietary restrictions. |

## Atypical antidepressants

| | |
|---|---|
| **Bupropion** | Inhibits NE and DA reuptake. Also used for smoking cessation. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizures in patients with bulimia and anorexia nervosa. ↓ risk of sexual side effects and weight gain compared to other antidepressants. |
| **Mirtazapine** | $\alpha_2$-antagonist (↑ release of NE and 5-HT), potent 5-$HT_2$ and 5-$HT_3$ receptor antagonist, and $H_1$ antagonist. Toxicity: sedation (which may be desirable in depressed patients with insomnia), ↑ appetite, weight gain (which may be desirable in underweight patients), dry mouth. |
| **Trazodone** | Primarily blocks 5-$HT_2$, $\alpha_1$-adrenergic, and $H_1$ receptors; also weakly inhibits 5-HT reuptake. Used primarily for insomnia, as high doses are needed for antidepressant effects. Toxicity: sedation, nausea, priapism, postural hypotension. Think tra**ZZZ**o**bone** due to sedative and male-specific side effects. |
| **Varenicline** | Nicotinic ACh receptor partial agonist. Used for smoking cessation. Toxicity: sleep disturbance. Vare**nicline** helps **ni**cotine cravings de**cline**. |
| **Vilazodone** | Inhibits 5-HT reuptake; 5-$HT_{1A}$ receptor partial agonist. Used for MDD. Toxicity: headache, diarrhea, nausea, anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents. |
| **Vortioxetine** | Inhibits 5-HT reuptake; 5-$HT_{1A}$ receptor agonist and 5-$HT_3$ receptor antagonist. Used for MDD. Toxicity: nausea, sexual dysfunction, sleep disturbances, anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents. |

## Opioid detoxification and relapse prevention

Intravenous drug users at ↑ risk for hepatitis, HIV, abscesses, bacteremia, right-heart endocarditis.

| | |
|---|---|
| **Methadone** | Long-acting oral opiate used for heroin detoxification or long-term maintenance therapy. |
| **Buprenorphine** | Sublingual form (partial agonist) used to prevent relapse. Can precipitate withdrawal symptoms when combined with full agonist. |
| **Naloxone** | Short-acting opioid antagonist given IM, IV, or as a nasal spray to treat acute opioid overdose, particularly to reverse respiratory and CNS depression. |
| **Naltrexone** | Long-acting oral opioid antagonist used after detoxification to prevent relapse. May help alcohol and nicotine cessation, weight loss. Use nal**trex**one for the long **trex** back to sobriety. |

HIGH-YIELD SYSTEMS

# Renal

*"But I know all about love already. I know precious little still about kidneys."*

—Aldous Huxley, *Antic Hay*

*"This too shall pass. Just like a kidney stone."*

—Hunter Madsen

*"I drink too much. The last time I gave a urine sample it had an olive in it."*

—Rodney Dangerfield

Being able to understand and apply renal physiology will be critical for the exam. Important topics include electrolyte disorders, acid-base derangements, glomerular disorders (including histopathology), acute and chronic kidney disease, urine casts, diuretics, ACE inhibitors, and AT II receptor blockers. Renal anomalies associated with various congenital defects are also high-yield associations to think about when evaluating pediatric vignettes.

## ▸ RENAL—EMBRYOLOGY

### Kidney embryology

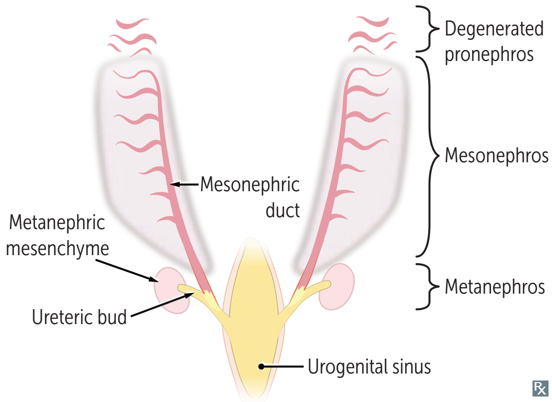
Pronephros—week 3 of development; then degenerates.

Mesonephros—week 4 of development; functions as interim kidney for 1st trimester; persists in the male genital system as Wolffian duct, forming ductus deferens and epididymis.

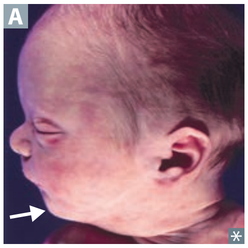
Metanephros—permanent; first appears in week 5 of development; nephrogenesis is normally completed by week 36 of gestation..

- Ureteric bud (metanephric diverticulum)—derived from caudal end of mesonephric duct; gives rise to ureter, pelvises, calyces, collecting ducts; fully canalized by week 10 of development
- Metanephric mesenchyme (ie, metanephric blastema)—ureteric bud interacts with this tissue; interaction induces differentiation and formation of glomerulus through to distal convoluted tubule (DCT)
- Aberrant interaction between these 2 tissues may result in several congenital malformations of the kidney (eg, renal agenesis, multicystic dysplastic kidney)

Ureteropelvic junction—last to canalize → congenital obstruction. Can be unilateral or bilateral. Most common pathologic cause of prenatal hydronephrosis. Detected by prenatal ultrasound.




### Potter sequence



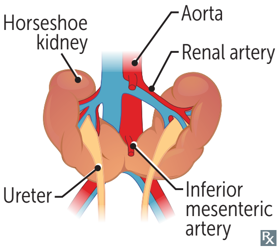

Oligohydramnios → compression of developing fetus → limb deformities, facial anomalies (eg, low-set ears and retrognathia A, flattened nose), compression of chest and lack of amniotic fluid aspiration into fetal lungs → pulmonary hypoplasia (cause of death).

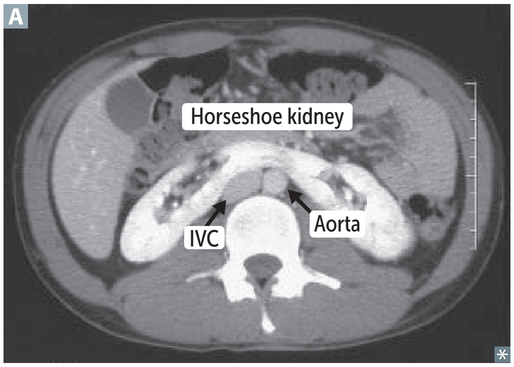
Caused by chronic placental insufficiency or reduced renal output, including ARPKD, obstructive uropathy (eg, posterior urethral valves), bilateral renal agenesis.

Babies who can't "Pee" in utero develop Potter sequence.

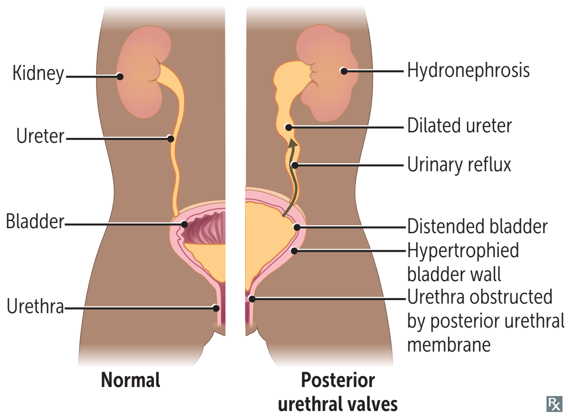
POTTER sequence associated with:
- Pulmonary hypoplasia
- Oligohydramnios (trigger)
- Twisted face
- Twisted skin
- Extremity defects
- Renal failure (in utero)

| | |
|---|---|
| **Horseshoe kidney** | Inferior poles of both kidneys fuse abnormally A. As they ascend from pelvis during fetal development, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen. Kidneys can function normally, but associated with hydronephrosis (eg, ureteropelvic junction obstruction), renal stones, infection, ↑ risk of renal cancer. Higher incidence in chromosomal aneuploidy (eg, Turner syndrome, trisomies 13, 18, 21). |



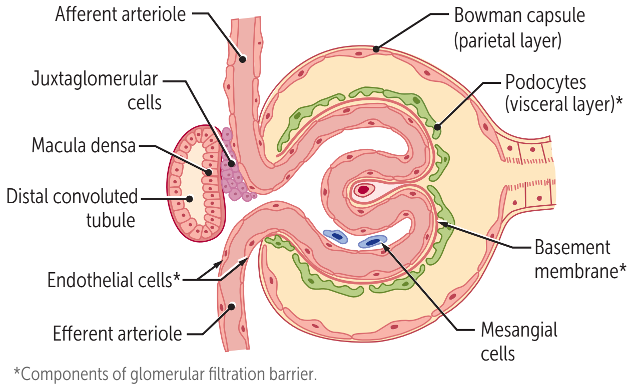

| | |
|---|---|
| **Congenital solitary functioning kidney** | Condition of being born with only one functioning kidney. Majority asymptomatic with compensatory hypertrophy of contralateral kidney, but anomalies in contralateral kidney are common. Often diagnosed prenatally via ultrasound. |
| **Unilateral renal agenesis** | Ureteric bud fails to develop and induce differentiation of metanephric mesenchyme → complete absence of kidney and ureter. |
| **Multicystic dysplastic kidney** | Ureteric bud develops, but fails to induce differentiation of metanephric mesenchyme → nonfunctional kidney consisting of cysts and connective tissue. Predominantly nonhereditary and usually unilateral; bilateral leads to Potter sequence. |
| **Duplex collecting system** | Bifurcation of ureteric bud before it enters the metanephric blastema creates a Y-shaped bifid ureter. Duplex collecting system can alternatively occur through two ureteric buds reaching and interacting with metanephric blastema. Strongly associated with vesicoureteral reflux and/or ureteral obstruction, ↑ risk for UTIs. Frequently presents with hydronephrosis. |
| **Posterior urethral valves** | Membrane remnant in the posterior (prostatic) urethra in males; its persistence can lead to urethral obstruction. Can be diagnosed prenatally by bilateral hydronephrosis and dilated or thick-walled bladder on ultrasound. Most common cause of bladder outlet obstruction in male infants. Associated with oligohydramnios in cases of severe obstruction. |




| | |
|---|---|
| **Vesicoureteral reflux** | Retrograde flow of urine from bladder toward upper urinary tract. Can be 1° due to abnormal/insufficient insertion of the ureter within the vesicular wall (ureterovesical junction [UVJ]) or 2° due to abnormally high bladder pressure resulting in retrograde flow via the UVJ. ↑ risk of recurrent UTIs. |

## ▸ RENAL—ANATOMY

### Kidney anatomy and glomerular structure



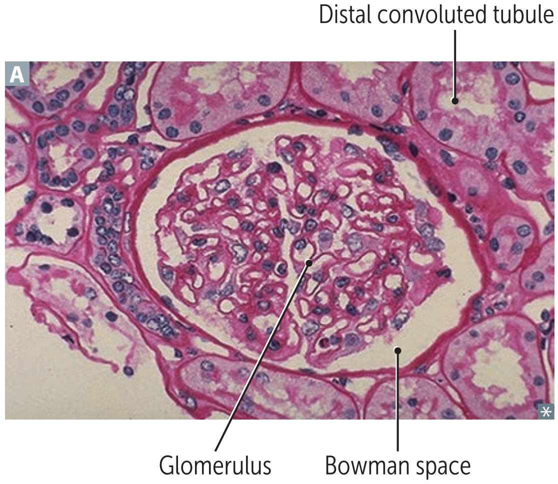

*Components of glomerular filtration barrier.

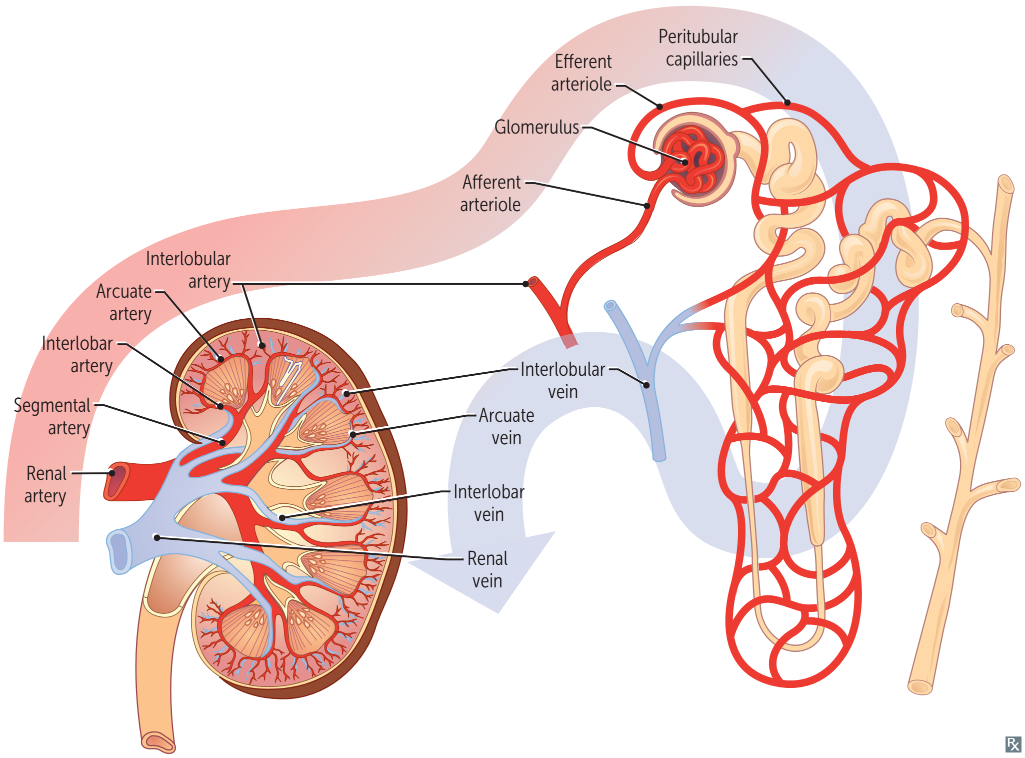
Cross-section of glomerulus A

Left renal vein receives two additional veins: left suprarenal and left gonadal veins.

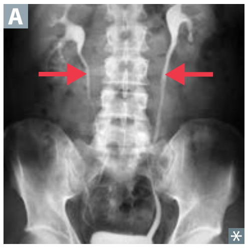
Despite high overall renal blood flow, renal medulla receives significantly less blood flow than renal cortex → very sensitive to hypoxia → vulnerable to ischemic damage.

Left kidney is taken during living donor transplantation because it has a longer renal vein.



### Course of ureters




Course of ureter A: arises from renal pelvis, travels under gonadal arteries → **over** common iliac artery → **under** uterine artery/vas deferens (retroperitoneal).

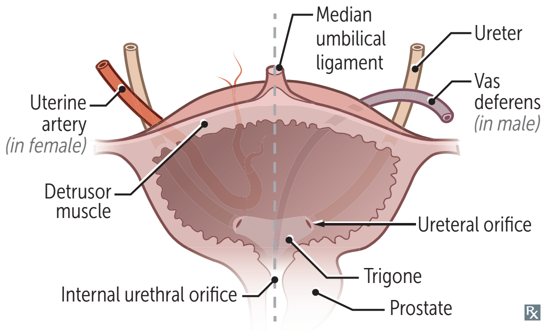
Gynecologic procedures (eg, ligation of uterine or ovarian vessels) may damage ureter → ureteral obstruction or leak.

Bladder contraction compresses the intramural ureter, preventing urine reflux.

Blood supply to ureter:
- Proximal—renal arteries
- Middle—gonadal artery, aorta, common and internal iliac arteries
- Distal—internal iliac and superior vesical arteries

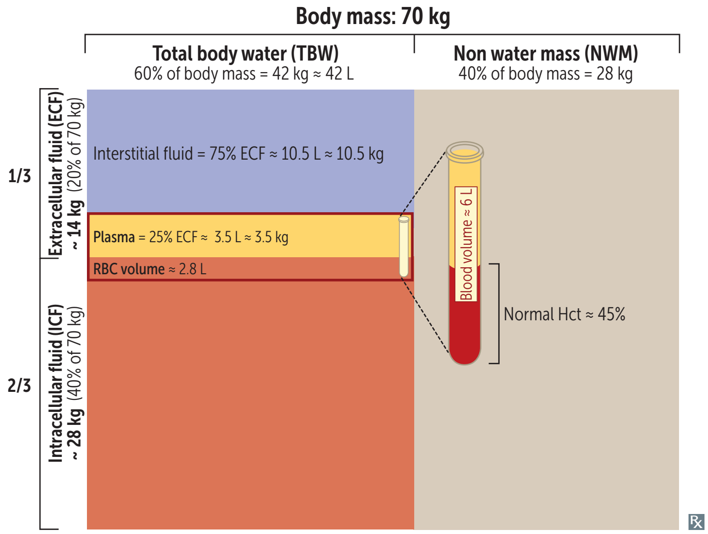
3 common points of ureteral obstruction: ureteropelvic junction, pelvic inlet, ureterovesical junction.

Water (ureters) flows **over** the iliacs and **under** the bridge (uterine artery or vas deferens).




## ▶ RENAL—PHYSIOLOGY

### Fluid compartments




**HIKIN'**: **HI**gh **K**$^+$ **IN**tracellularly.

60–40–20 rule (% of body weight for average person):
- 60% total body water
- 40% ICF, mainly composed of $K^+$, $Mg^{2+}$, organic phosphates (eg, ATP)
- 20% ECF, mainly composed of $Na^+$, $Cl^-$, $HCO_3^-$, albumin

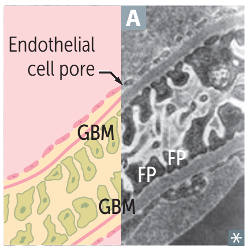
Plasma volume can be measured by radiolabeling albumin.

Extracellular volume can be measured by inulin or mannitol.

Serum osmolality = 275–295 mOsm/kg $H_2O$.

Plasma volume = TBV × (1 – Hct).

### Glomerular filtration barrier




Responsible for filtration of plasma according to size and charge selectivity.

Composed of:
- Fenestrated capillary endothelium
- Basement membrane with type IV collagen chains and heparan sulfate
- Visceral epithelial layer consisting of podocyte foot processes (FPs) A

Charger barrier—glomerular filtration barrier contains ⊖ charged glycoproteins that prevent entry of ⊖ charged molecules (eg, albumin).

Size barrier—fenestrated capillary endothelium (prevents entry of > 100 nm molecules/blood cells); podocyte foot processes interpose with glomerular basement membrane (GBM); slit diaphragm (prevents entry of molecules > 4–5 nm).

## Renal clearance

$C_x = (U_xV)/P_x$ = volume of plasma from which the substance is completely cleared in the urine per unit time.

If $C_x <$ GFR: net tubular reabsorption and/or not freely filtered.

If $C_x >$ GFR: net tubular secretion of X.

If $C_x =$ GFR: no net secretion or reabsorption.

$C_x$ = clearance of X (mL/min).

$U_x$ = urine concentration of X (eg, mg/mL).

$P_x$ = plasma concentration of X (eg, mg/mL).

V = urine flow rate (mL/min).

## Glomerular filtration rate

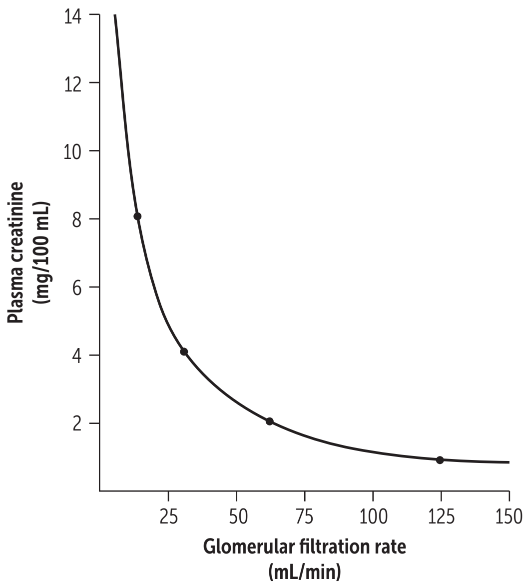
Inulin clearance can be used to calculate GFR because it is freely filtered and is neither reabsorbed nor secreted.

$$C_{inulin} = GFR = U_{inulin} \times V/P_{inulin}$$
$$= K_f\,[(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$$

(GC = glomerular capillary; BS = Bowman space; $\pi_{BS}$ normally equals zero; $K_f$ = filtration coefficient).

Normal GFR ≈ 100 mL/min.

Creatinine clearance is an approximate measure of GFR. Slightly overestimates GFR because creatinine is moderately secreted by renal tubules.




## Effective renal plasma flow

Effective renal plasma flow (eRPF) can be estimated using *para*-aminohippuric acid (PAH) clearance. Between filtration and secretion, there is nearly 100% excretion of all PAH that enters the kidney.

eRPF = $U_{PAH} \times V/P_{PAH} = C_{PAH}$.

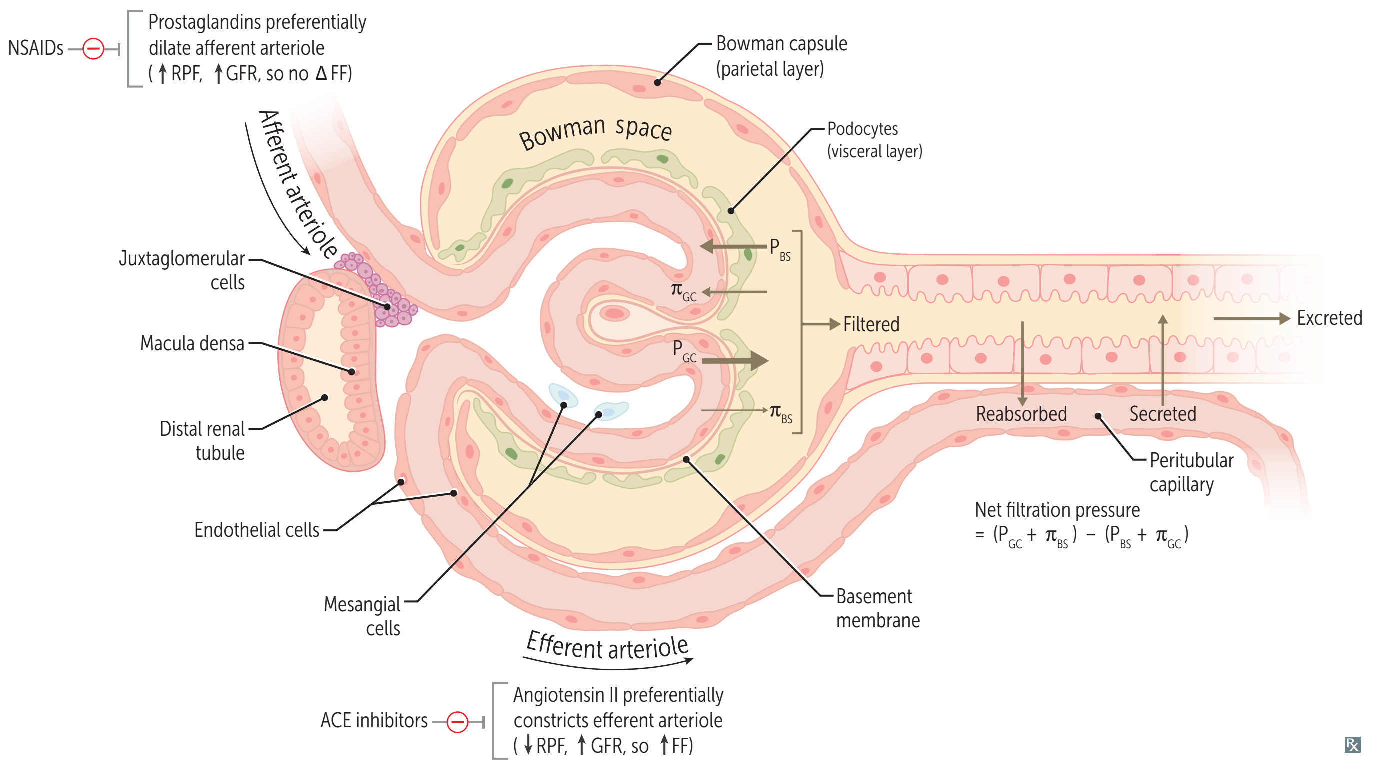
Renal blood flow (RBF) = RPF/(1 – Hct). Usually 20–25% of cardiac output, remaining constant due to autoregulation.

eRPF underestimates true renal plasma flow (RPF) slightly.

**Filtration**

Filtration fraction (FF) = GFR/RPF.
Normal FF = 20%.
Filtered load (mg/min) = GFR (mL/min) × plasma concentration (mg/mL).

GFR can be estimated with creatinine clearance.
RPF is best estimated with PAH clearance.
**P**rostaglandins **D**ilate **A**fferent arteriole (**PDA**).
**A**ngiotensin II **C**onstricts **E**fferent arteriole (**ACE**).




**Changes in glomerular dynamics**

| | GFR | RPF | FF (GFR/RPF) |
|---|---|---|---|
| Afferent arteriole constriction | ↓ | ↓ | — |
| Efferent arteriole constriction | ↑ | ↓ | ↑ |
| ↑ plasma protein concentration | ↓ | — | ↓ |
| ↓ plasma protein concentration | ↑ | — | ↑ |
| Constriction of ureter | ↓ | — | ↓ |
| Dehydration | ↓ | ↓↓ | ↑ |

**Calculation of reabsorption and secretion rate**

Filtered load = GFR × $P_x$.
Excretion rate = V × $U_x$.
Reabsorption rate = filtered – excreted.
Secretion rate = excreted – filtered.
$Fe_{Na}$ = fractional excretion of sodium.

$$Fe_{Na} = \frac{Na^+ \text{ excreted}}{Na^+ \text{ filtered}} = \frac{V \times U_{Na}}{GFR \times P_{Na}} = \frac{P_{Cr} \times U_{Na}}{U_{Cr} \times P_{Na}} \text{ where } GFR = \frac{U_{Cr} \times V}{P_{Cr}}$$

---

**Glucose clearance**

Glucose at a normal plasma level (range 60–120 mg/dL) is completely reabsorbed in proximal convoluted tubule (PCT) by $Na^+$/glucose cotransport.

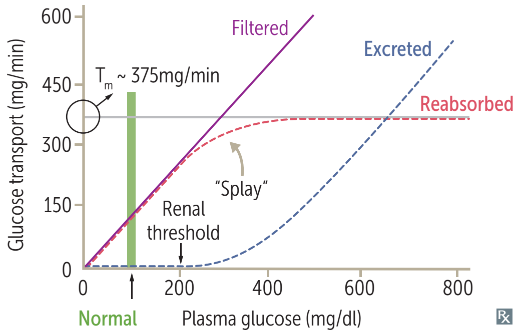
In adults, at plasma glucose of ~ 200 mg/dL, glucosuria begins (threshold). At rate of ~ 375 mg/min, all transporters are fully saturated ($T_m$).

Normal pregnancy is associated with ↑ GFR. With ↑ filtration of all substances, including glucose, the glucose threshold occurs at lower plasma glucose concentrations → glucosuria at normal plasma glucose levels.

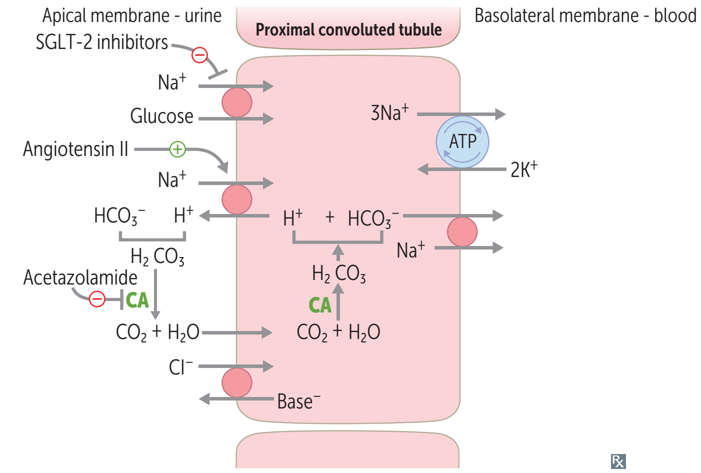
Sodium-glucose cotransporter 2 (SGLT2) inhibitors (eg, -flozin drugs) result in glucosuria at plasma concentrations < 200 mg/dL.

Glucosuria is an important clinical clue to diabetes mellitus.

Splay phenomenon—$T_m$ for glucose is reached gradually rather than sharply due to the heterogeneity of nephrons (ie, different $T_m$ points); represented by the portion of the titration curve between threshold and $T_m$.



## Nephron transport physiology



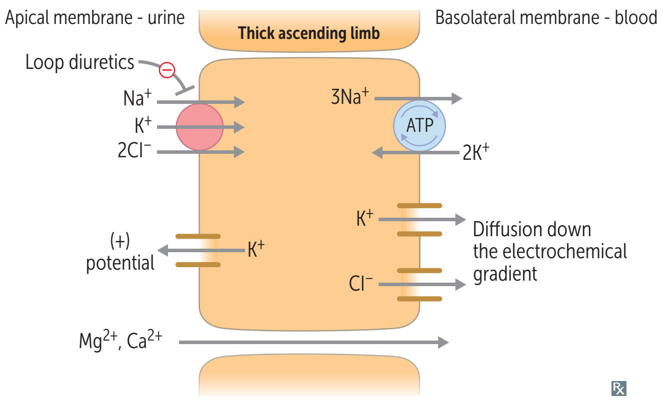

**Early PCT**—contains brush border. Reabsorbs all glucose and amino acids and most $HCO_3^-$, $Na^+$, $Cl^-$, $PO_4^{3-}$, $K^+$, $H_2O$, and uric acid. Isotonic absorption. Generates and secretes $NH_3$, which enables the kidney to secrete more $H^+$.

PTH—inhibits $Na^+/PO_4^{3-}$ cotransport → ↑ $PO_4^{3-}$ excretion.

AT II—stimulates $Na^+/H^+$ exchange → ↑ $Na^+$, $H_2O$, and $HCO_3^-$ reabsorption (permitting contraction alkalosis).

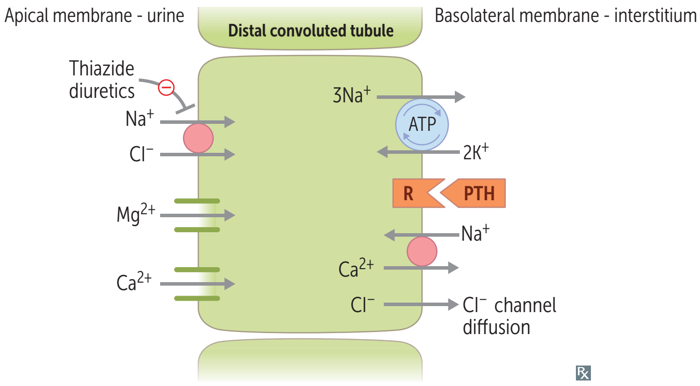
65–80% $Na^+$ and $H_2O$ reabsorbed.

**Thin descending loop of Henle**—passively reabsorbs $H_2O$ via medullary hypertonicity (impermeable to $Na^+$). Concentrating segment. Makes urine hypertonic.




**Thick ascending loop of Henle**—reabsorbs $Na^+$, $K^+$, and $Cl^-$. Indirectly induces paracellular reabsorption of $Mg^{2+}$ and $Ca^{2+}$ through ⊕ lumen potential generated by $K^+$ backleak. Impermeable to $H_2O$. Makes urine less concentrated as it ascends.

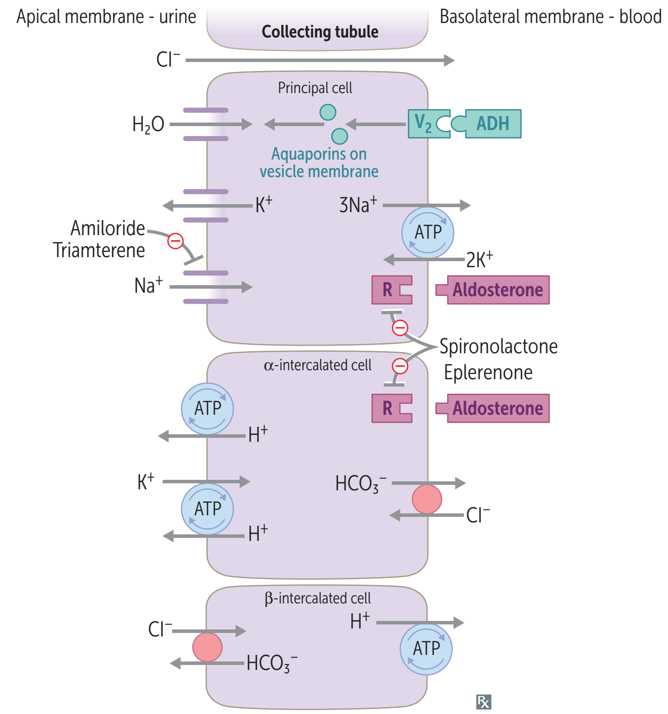
10–20% $Na^+$ reabsorbed.




**Early DCT**—reabsorbs $Na^+$, $Cl^-$. Impermeable to $H_2O$. Makes urine fully dilute (hypotonic).

PTH—↑ $Ca^{2+}/Na^+$ exchange → ↑ $Ca^{2+}$ reabsorption.

5–10% $Na^+$ reabsorbed.




**Collecting tubule**—reabsorbs $Na^+$ in exchange for secreting $K^+$ and $H^+$ (regulated by aldosterone).

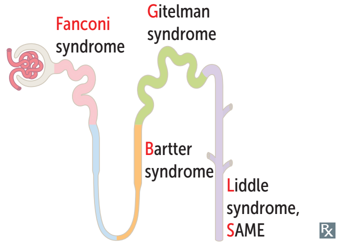
Aldosterone—acts on mineralocorticoid receptor → mRNA → protein synthesis. In principal cells: ↑ apical $K^+$ conductance, ↑ $Na^+/K^+$ pump, ↑ epithelial $Na^+$ channel (ENaC) activity → lumen negativity → $K^+$ secretion. In α-intercalated cells: lumen negativity → ↑ $H^+$ ATPase activity → ↑ $H^+$ secretion → ↑ $HCO_3^-/Cl^-$ exchanger activity.

ADH—acts at $V_2$ receptor → insertion of aquaporin $H_2O$ channels on apical side.

3–5% $Na^+$ reabsorbed.

## Renal tubular defects

Order: Fanconi's BaGeLS



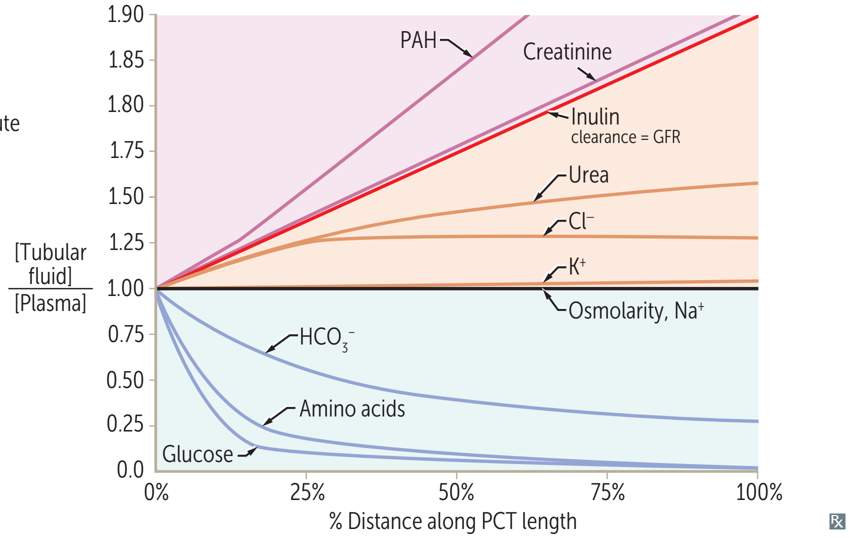

| | DEFECTS | EFFECTS | CAUSES | NOTES |
|---|---|---|---|---|
| **Fanconi syndrome** | Generalized reabsorption defect in PCT → ↑ excretion of amino acids, glucose, $HCO_3^-$, and $PO_4^{3-}$, and all substances reabsorbed by the PCT | Metabolic acidosis (proximal RTA), hypophosphatemia, hypokalemia | Hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease), ischemia, multiple myeloma, nephrotoxins/drugs (eg, ifosfamide, cisplatin), lead poisoning | Growth retardation and rickets/osteopenia common due to hypophosphatemia<br>Volume depletion also common |
| **Bartter syndrome** | Reabsorption defect in thick ascending loop of Henle (affects $Na^+/K^+/2Cl^-$ cotransporter) | Metabolic alkalosis, hypokalemia, hypercalciuria | Autosomal recessive | Presents similarly to chronic loop diuretic use |
| **Gitelman syndrome** | Reabsorption defect of NaCl in DCT | Metabolic alkalosis, hypomagnesemia, hypokalemia, hypocalciuria | Autosomal recessive | Presents similarly to lifelong thiazide diuretic use<br>Less severe than Bartter syndrome |
| **Liddle syndrome** | Gain of function mutation → ↓ $Na^+$ channel degradation → ↑ $Na^+$ reabsorption in collecting tubules | Metabolic alkalosis, hypokalemia, hypertension, ↓ aldosterone | Autosomal dominant | Presents similarly to hyperaldosteronism, but aldosterone is nearly undetectable<br>Treatment: amiloride |
| **Syndrome of Apparent Mineralocorticoid Excess** | Cortisol activates mineralocorticoid receptors; 11β-HSD converts cortisol to cortisone (inactive on these receptors)<br>Hereditary 11β-HSD deficiency → ↑ cortisol → ↑ mineralocorticoid receptor activity | Metabolic alkalosis, hypokalemia, hypertension<br>↓ serum aldosterone level; cortisol tries to be the SAME as aldosterone | Autosomal recessive<br>Can acquire disorder from glycyrrhetinic acid (present in licorice), which blocks activity of 11β-hydroxysteroid dehydrogenase | Treatment: $K^+$-sparing diuretics (↓ mineralocorticoid effects) or corticosteroids (exogenous corticosteroid ↓ endogenous cortisol production → ↓ mineralocorticoid receptor activation) |

**Relative concentrations along proximal convoluted tubules**

[TF/P] > 1
when solute is reabsorbed less quickly than water or when solute is secreted

[TF/P] = 1
when solute and water are reabsorbed at the same rate

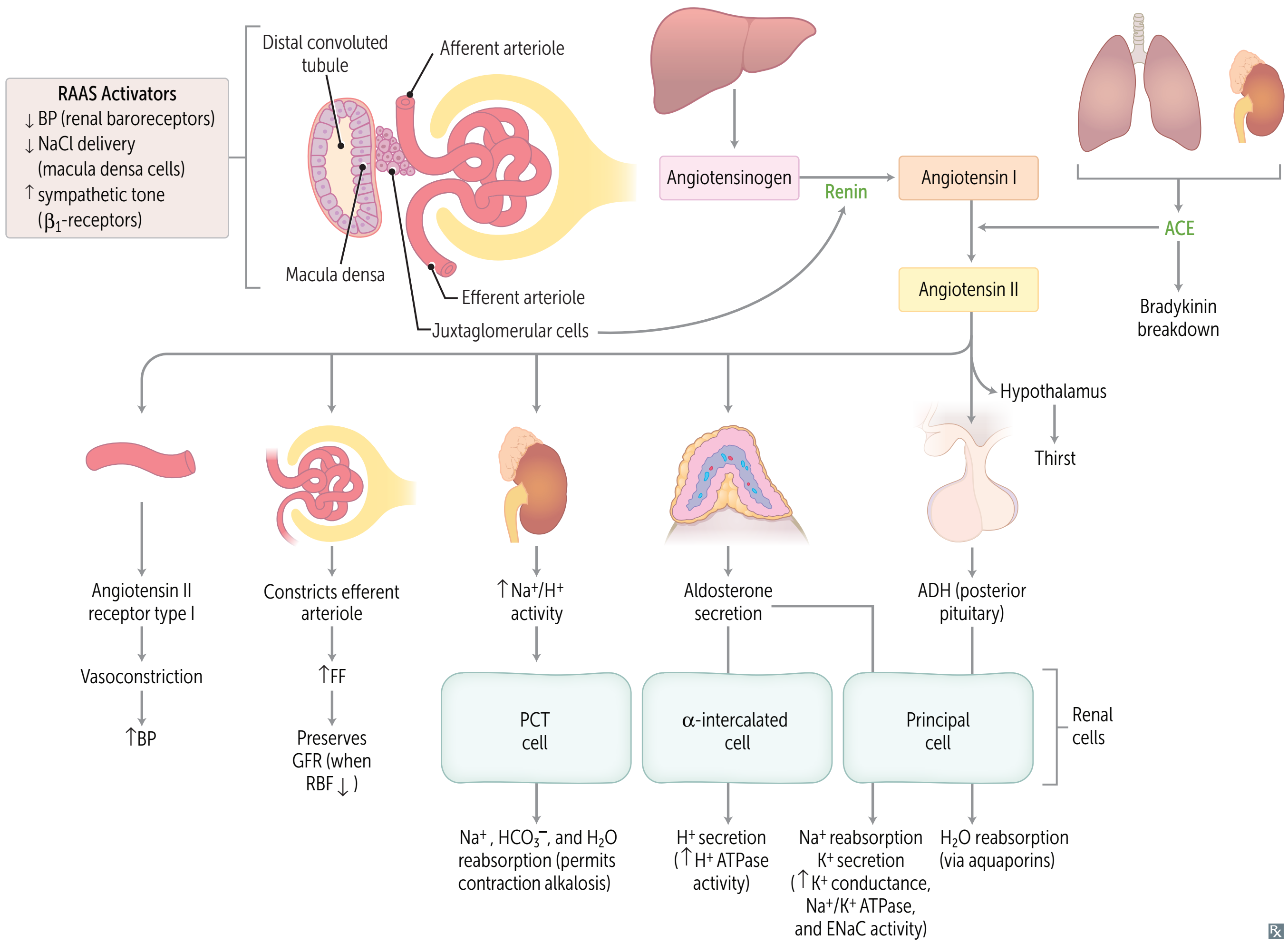
[TF/P] < 1
when solute is reabsorbed more quickly than water




Tubular inulin ↑ in concentration (but not amount) along the PCT as a result of water reabsorption.

$Cl^-$ reabsorption occurs at a slower rate than $Na^+$ in early PCT and then matches the rate of $Na^+$ reabsorption more distally. Thus, its relative concentration ↑ before it plateaus.

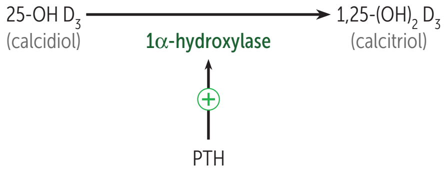
### Renin-angiotensin-aldosterone system




| | |
|---|---|
| **Renin** | Secreted by JG cells in response to ↓ renal perfusion pressure (detected by renal baroreceptors in afferent arteriole), ↑ renal sympathetic discharge ($\beta_1$ effect), and ↓ NaCl delivery to macula densa cells. |
| **ACE** | Catalyzes conversion of angiotensin I to angiotensin II. Located in many tissues but conversion occurs most extensively in the lung. Produced by vascular endothelial cells in the lung. |
| **AT II** | Helps maintain blood volume and blood pressure. Affects baroreceptor function; limits reflex bradycardia, which would normally accompany its pressor effects. |
| **ANP, BNP** | Released from atria (ANP) and ventricles (BNP) in response to ↑ volume; inhibits renin-angiotensin-aldosterone system; relaxes vascular smooth muscle via cGMP → ↑ GFR, ↓ renin. Dilates afferent arteriole, promotes natriuresis. |
| **ADH (vasopressin)** | Primarily regulates serum osmolality; also responds to low blood volume states. Stimulates reabsorption of water in collecting ducts. Also stimulates reabsorption of urea in collecting ducts to maximize corticopapillary osmotic gradient. |
| **Aldosterone** | Primarily regulates ECF volume and $Na^+$ content; ↑ release in hypovolemic states. Responds to hyperkalemia by ↑ $K^+$ excretion. |

| | | |
|---|---|---|
| **Juxtaglomerular apparatus** | Consists of mesangial cells, JG cells (modified smooth muscle of afferent arteriole), and the macula densa (NaCl sensor located at the DCT). JG cells secrete renin in response to ↓ renal blood pressure and ↑ sympathetic tone ($\beta_1$). Macula densa cells sense ↓ NaCl delivery to DCT → ↑ renin release → efferent arteriole vasoconstriction → ↑ GFR. | JGA maintains GFR via renin-angiotensin-aldosterone system.<br>In addition to vasodilatory properties, β-blockers can decrease BP by inhibiting $\beta_1$-receptors of the JGA → ↓ renin release. |

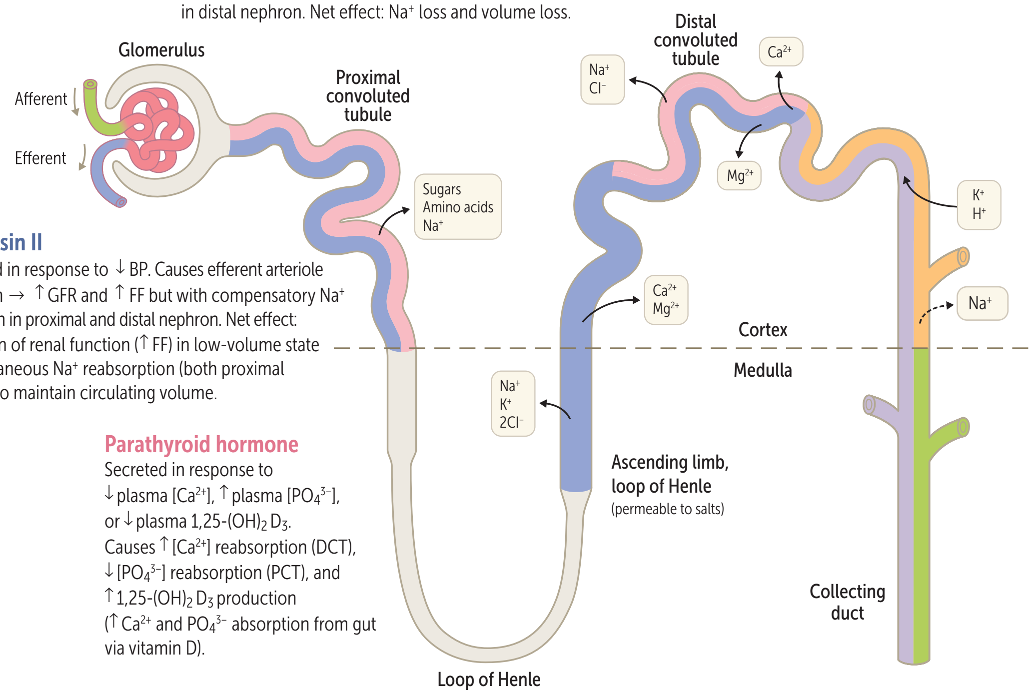
## Kidney hormone functions

| | | |
|---|---|---|
| **Erythropoietin** | Released by interstitial cells in peritubular capillary bed in response to hypoxia. | Stimulates RBC proliferation in bone marrow.<br>Administered for anemia secondary to chronic kidney disease. ↑ risk of HTN. |
| **Calciferol (vitamin D)** | PCT cells convert 25-OH vitamin $D_3$ to 1,25-$(OH)_2$ vitamin $D_3$ (calcitriol, active form). Increases calcium absorption in small bowel. |  |
| **Prostaglandins** | Paracrine secretion vasodilates afferent arterioles to ↑ RBF. | NSAIDs block renal-protective prostaglandin synthesis → constriction of afferent arteriole and ↓ GFR; this may result in acute kidney injury in low renal blood flow states. |
| **Dopamine** | Secreted by PCT cells, promotes natriuresis. At low doses; dilates interlobular arteries, afferent arterioles, efferent arterioles → ↑ RBF, little or no change in GFR. At higher doses; acts as vasoconstrictor. | |

## Hormones acting on kidney

### Atrial natriuretic peptide

Secreted in response to ↑ atrial pressure. Causes ↑ GFR and ↑ $Na^+$ filtration with no compensatory $Na^+$ reabsorption in distal nephron. Net effect: $Na^+$ loss and volume loss.




### Angiotensin II

Synthesized in response to ↓ BP. Causes efferent arteriole constriction → ↑ GFR and ↑ FF but with compensatory $Na^+$ reabsorption in proximal and distal nephron. Net effect: preservation of renal function (↑ FF) in low-volume state with simultaneous $Na^+$ reabsorption (both proximal and distal) to maintain circulating volume.

### Parathyroid hormone

Secreted in response to ↓ plasma [$Ca^{2+}$], ↑ plasma [$PO_4^{3-}$], or ↓ plasma 1,25-$(OH)_2$ $D_3$. Causes ↑ [$Ca^{2+}$] reabsorption (DCT), ↓ [$PO_4^{3-}$] reabsorption (PCT), and ↑ 1,25-$(OH)_2$ $D_3$ production (↑ $Ca^{2+}$ and $PO_4^{3-}$ absorption from gut via vitamin D).

### Aldosterone

Secreted in response to ↓ blood volume (via AT II) and ↑ plasma [$K^+$]; causes ↑ $Na^+$ reabsorption, ↑ $K^+$ secretion, ↑ $H^+$ secretion.

### ADH (vasopressin)

Secreted in response to ↑ plasma osmolarity and ↓ blood volume. Binds to receptors on principal cells, causing ↑ number of aquaporins and ↑ $H_2O$ reabsorption.

↑ reabsorption of urea in collecting ducts to maximize corticopapillary osmotic gradient.

## Potassium shifts

| SHIFTS $K^+$ INTO CELL (CAUSING HYPOKALEMIA) | SHIFTS $K^+$ OUT OF CELL (CAUSING HYPERKALEMIA) |
|---|---|
| | **D**igoxin (blocks $Na^+/K^+$ ATPase) |
| Hypo-osmolarity | Hyper**O**smolarity |
| | **L**ysis of cells (eg, crush injury, rhabdomyolysis, tumor lysis syndrome) |
| Alkalosis | **A**cidosis |
| β-adrenergic agonist (↑ $Na^+/K^+$ ATPase) | **β**-blocker |
| Insulin (↑ $Na^+/K^+$ ATPase) | High blood **S**ugar (insulin deficiency) |
| **In**sulin shifts $K^+$ **in**to cells | **S**uccinylcholine (↑ risk in burns/muscle trauma) |
| | Hyperkalemia? **DO LAβSS** |

## Electrolyte disturbances

| ELECTROLYTE | LOW SERUM CONCENTRATION | HIGH SERUM CONCENTRATION |
|---|---|---|
| **Sodium** | Nausea, malaise, stupor, coma, seizures | Irritability, stupor, coma |
| **Potassium** | U waves and flattened T waves on ECG, arrhythmias, muscle cramps, spasm, weakness | Wide QRS and peaked T waves on ECG, arrhythmias, muscle weakness |
| **Calcium** | Tetany, seizures, QT prolongation, twitching (eg, Chvostek sign), spasm (eg, Trousseau sign) | **Stones** (renal), **bones** (pain), **groans** (abdominal pain), **thrones** (↑ urinary frequency), **psychiatric overtones** (anxiety, altered mental status) |
| **Magnesium** | Tetany, torsades de pointes, hypokalemia, hypocalcemia (when $[Mg^{2+}] < 1.0$ mEq/L) | ↓ DTRs, lethargy, bradycardia, hypotension, cardiac arrest, hypocalcemia |
| **Phosphate** | Bone loss, osteomalacia (adults), rickets (children) | Renal stones, metastatic calcifications, hypocalcemia |

## Features of renal disorders

| CONDITION | BLOOD PRESSURE | PLASMA RENIN | ALDOSTERONE | SERUM $Mg^{2+}$ | URINE $Ca^{2+}$ |
|---|---|---|---|---|---|
| **SIADH** | —/↑ | ↓ | ↓ | — | — |
| **Primary hyperaldosteronism** | ↑ | ↓ | **↑** | — | — |
| **Renin-secreting tumor** | ↑ | **↑** | ↑ | — | — |
| **Bartter syndrome** | — | ↑ | ↑ | — | **↑** |
| **Gitelman syndrome** | — | ↑ | ↑ | ↓ | **↓** |
| **Liddle syndrome, syndrome of apparent mineralocorticoid excess** | ↑ | ↓ | **↓** | — | — |

**↑ ↓** = important differentiating feature.

## Acid-base physiology

| | pH | $P_{CO_2}$ | $[HCO_3^-]$ | COMPENSATORY RESPONSE |
|---|---|---|---|---|
| **Metabolic acidosis** | ↓ | ↓ (red) | ↓ | Hyperventilation (immediate) |
| **Metabolic alkalosis** | ↑ | ↑ (red) | ↑ | Hypoventilation (immediate) |
| **Respiratory acidosis** | ↓ | ↑ | ↑ (red) | ↑ renal $[HCO_3^-]$ reabsorption (delayed) |
| **Respiratory alkalosis** | ↑ | ↓ | ↓ (red) | ↓ renal $[HCO_3^-]$ reabsorption (delayed) |

Key: ↓ ↑ = compensatory response.

$$\text{Henderson-Hasselbalch equation: } pH = 6.1 + \log \frac{[HCO_3^-]}{0.03\ P_{CO_2}}$$

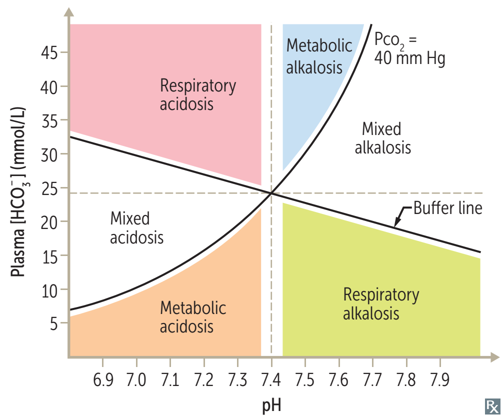
Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winters formula. If measured $P_{CO_2}$ > predicted $P_{CO_2}$ → concomitant respiratory acidosis; if measured $P_{CO_2}$ < predicted $P_{CO_2}$ → concomitant respiratory alkalosis:

$$P_{CO_2} = 1.5\ [HCO_3^-] + 8 \pm 2$$

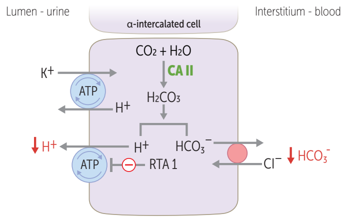
## Acidosis and alkalosis

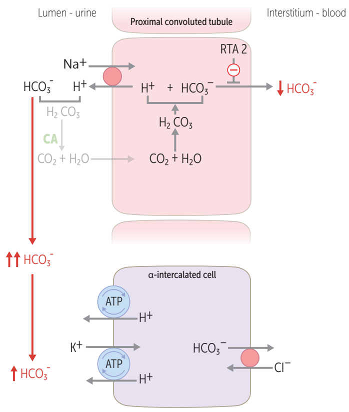
**Check arterial pH**

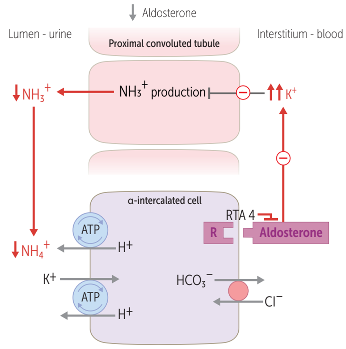
- pH < 7.35 → **Acidemia**
  - $P_{CO_2}$ > 44 mm Hg → **Respiratory acidosis**
    - **Hypoventilation**
      - Airway obstruction
      - Acute lung disease
      - Chronic lung disease
      - Opioids, sedatives
      - Weakening of respiratory muscles
  - $HCO_3^-$ < 20 mEq/L → **Metabolic acidosis**
    - **Check anion gap** = $Na^+ - (Cl^- + HCO_3^-)$
      - > 12 mEq/L → **↑ Anion gap**
        - GOLDMARK:
        - Glycols (ethylene glycol, proplyene glycol)
        - Oxoproline (toxic metabolite of acetaminophen)
        - L-lactate (lactic acidosis)
        - D-lactate (exogenous lactic acid)
        - Methanol (and other alcohols)
        - Aspirin (late effect)
        - Renal failure
        - Keytones (diabetic, alcoholic, starvation)
      - 8–12 mEq/L → **Normal anion gap**
        - HARDASS
        - Hyperchloremia/hyperalimentation
        - Addison disease
        - Renal tubular acidosis
        - Diarrhea
        - Acetazolamide
        - Spironolactone
        - Saline infusion
- pH > 7.45 → **Alkalemia**
  - $P_{CO_2}$ < 36 mm Hg → **Respiratory alkalosis**
    - **Hyperventilation**
      - Anxiety/panic attack
      - Hypoxemia (eg, high altitude)
      - Salicylates (early)
      - Tumor
      - Pulmonary embolism
      - Pregnancy
  - $HCO_3^-$ > 28 mEq/L → **Metabolic alkalosis**
    - **$H^+$ loss/$HCO_3^-$ excess**
      - Loop diuretics
      - Vomiting
      - Antacid use
      - Hyperaldosteronism



## Renal tubular acidosis



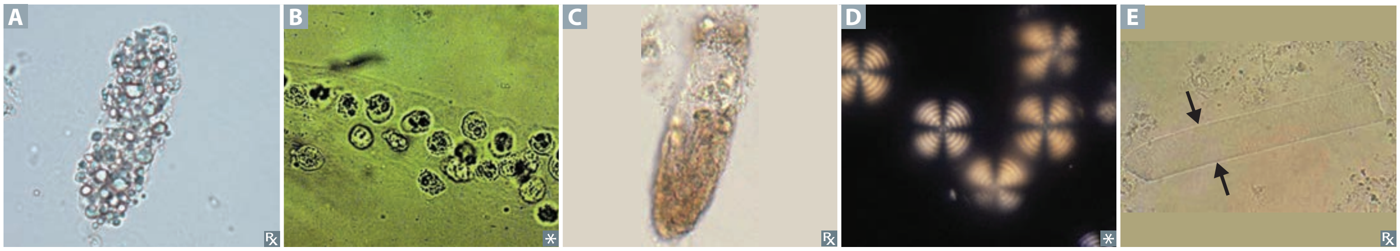




| | Distal renal tubular acidosis (RTA type 1) | Proximal renal tubular acidosis (RTA type 2) | Hyperkalemic tubular acidosis (RTA type 4) |
|---|---|---|---|
| DEFECT | Inability of α-intercalated cells to secrete $H^+$ → no new $HCO_3^-$ is generated → metabolic acidosis | Defect in PCT $HCO_3^-$ reabsorption → ↑ excretion of $HCO_3^-$ in urine → metabolic acidosis<br>Urine can be acidified by α-intercalated cells in collecting duct, but not enough to overcome ↑ $HCO_3^-$ excretion | Hypoaldosteronism or aldosterone resistance; hyperkalemia → ↓ $NH_3$ synthesis in PCT → ↓ $NH_4^+$ excretion |
| URINE pH | > 5.5 | < 5.5 when plasma $HCO_3^-$ below reduced resorption threshold<br>> 5.5 when filtered $HCO_3^-$ exceeds resorptive threshold | < 5.5 (or variable) |
| SERUM $K^+$ | ↓ | ↓ | ↑ |
| CAUSES | Amphotericin B toxicity, analgesic nephropathy, congenital anomalies (obstruction) of urinary tract, autoimmune diseases (eg, SLE) | Fanconi syndrome, multiple myeloma, carbonic anhydrase inhibitors | ↓ aldosterone production (eg, diabetic hyporeninism, ACE inhibitors, ARB, NSAIDs, heparin, cyclosporine, adrenal insufficiency) or aldosterone resistance (eg, $K^+$-sparing diuretics, nephropathy due to obstruction, TMP-SMX) |
| ASSOCIATIONS | ↑ risk for calcium phosphate kidney stones (due to ↑ urine pH and ↑ bone turnover related to buffering) | ↑ risk for hypophosphatemic rickets (in Fanconi syndrome) | |

## ▶ RENAL—PATHOLOGY

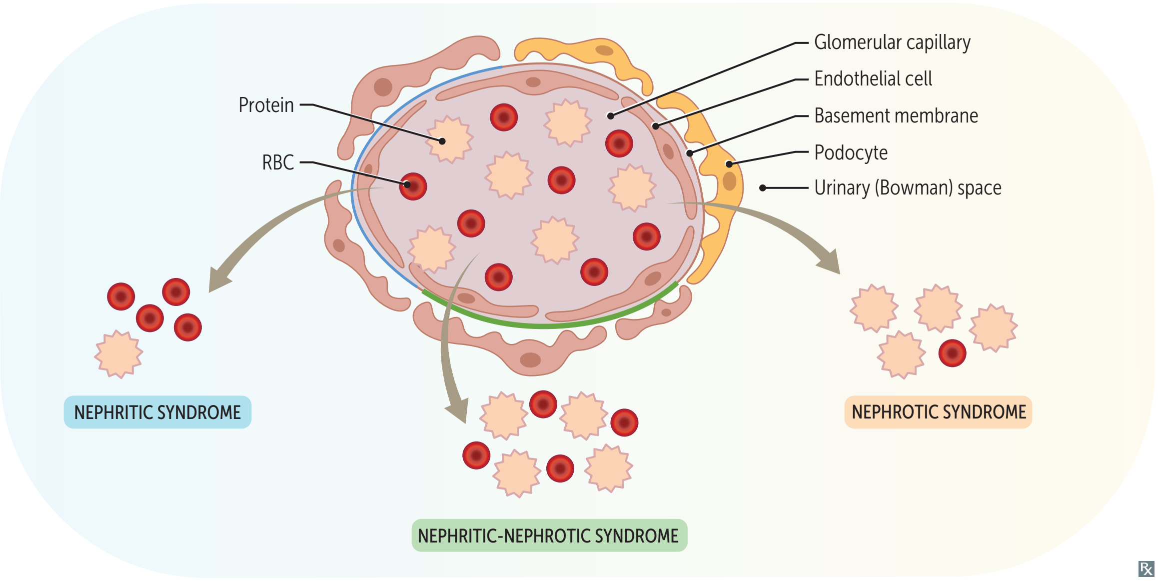
| | |
|---|---|
| **Casts in urine** | Presence of casts indicates that hematuria/pyuria is of glomerular or renal tubular origin.<br>Bladder cancer, kidney stones → hematuria, no casts.<br>Acute cystitis → pyuria, no casts. |
| **RBC casts** A | Glomerulonephritis, hypertensive emergency. |
| **WBC casts** B | Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection. |
| **Granular casts** C | Acute tubular necrosis (ATN). Can be "muddy brown" in appearance. |
| **Fatty casts ("oval fat bodies")** | Nephrotic syndrome. Associated with "Maltese cross" sign D. |
| **Waxy casts** | End-stage renal disease/chronic kidney disease. |
| **Hyaline casts** E | Nonspecific, can be a normal finding with dehydration, exercise, or diuretic therapy. Form via solidification of Tamm-Horsfall mucoprotein (uromodulin), secreted by renal tubular cells to prevent UTIs. |




### Nomenclature of glomerular disorders

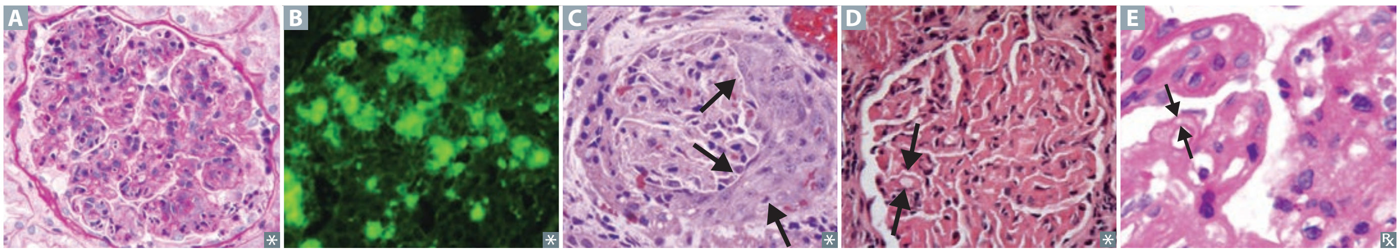
| TYPE | CHARACTERISTICS | EXAMPLE |
|---|---|---|
| **Focal** | < 50% of glomeruli are involved | Focal segmental glomerulosclerosis |
| **Diffuse** | > 50% of glomeruli are involved | Diffuse proliferative glomerulonephritis |
| **Proliferative** | Hypercellular glomeruli | Membranoproliferative glomerulonephritis |
| **Membranous** | Thickening of glomerular basement membrane (GBM) | Membranous nephropathy |
| **Primary glomerular disease** | 1° disease of the kidney specifically impacting the glomeruli | Minimal change disease |
| **Secondary glomerular disease** | Systemic disease or disease of another organ system that also impacts the glomeruli | SLE, diabetic nephropathy |

## Glomerular diseases

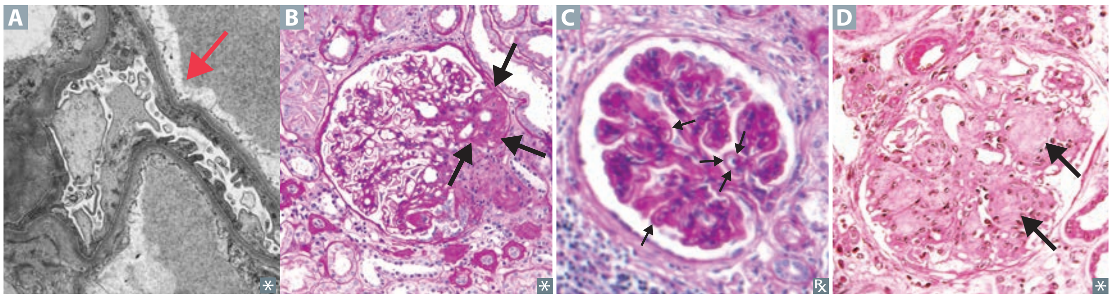



| TYPE | ETIOLOGY | CLINICAL PRESENTATION | EXAMPLES |
|---|---|---|---|
| **Nephritic syndrome** | Glomerular inflammation → GBM damage → loss of RBCs into urine → dysmorphic RBCs, hematuria | Hematuria, RBC casts in urine<br>↓ GFR → oliguria, azotemia<br>↑ renin release, HTN<br>Proteinuria often in the subnephrotic range (< 3.5 g/day) but in severe cases may be in nephrotic range | ▪ Acute poststreptococcal glomerulonephritis<br>▪ Goodpasture syndrome<br>▪ IgA nephropathy (Berger disease)<br>▪ Alport syndrome<br>▪ Membranoproliferative glomerulonephritis |
| **Nephrotic syndrome** | Podocyte damage → impaired charge barrier → proteinuria | Massive proteinuria (> 3.5 g/day) with hypoalbuminemia, edema<br>Frothy urine with fatty casts<br>Associated with hypercoagulable state due to antithrombin III loss in urine and ↑ risk of infection (loss of IgGs in urine and soft tissue compromise by edema) | May be 1° (eg, direct podocyte damage) or 2° (podocyte damage from systemic process):<br>▪ Focal segmental glomerulosclerosis (1° or 2°)<br>▪ Minimal change disease (1° or 2°)<br>▪ Membranous nephropathy (1° or 2°)<br>▪ Amyloidosis (2°)<br>▪ Diabetic glomerulonephropathy (2°) |
| **Nephritic-nephrotic syndrome** | Severe GBM damage → loss of RBCs into urine + impaired charge barrier → hematuria + proteinuria | Nephrotic-range proteinuria (> 3.5 g/day) and concomitant features of nephritic syndrome | Can occur with any form of nephritic syndrome, but is most common with:<br>▪ Diffuse proliferative glomerulonephritis<br>▪ Membranoproliferative glomerulonephritis |

| Nephritic syndrome | Nephritic syndrome = inflammatory process. |
|---|---|
| Acute poststreptococcal glomerulonephritis | Most frequently seen in children. ~ 2–4 weeks after group A streptococcal infection of pharynx or skin. Also called postinfectious glomerulonephritis when caused by non-streptococcal pathogens. Resolves spontaneously in most children; may progress to renal insufficiency in adults. Type III hypersensitivity reaction. Presents with peripheral and periorbital edema, tea or cola-colored urine, HTN. ⊕ strep titers/serologies, ↓ complement levels (C3) due to consumption.<br>▪ LM—glomeruli enlarged and hypercellular A<br>▪ IF—(“starry sky”) granular appearance (“lumpy-bumpy”) B due to IgG, IgM, and C3 deposition along GBM and mesangium<br>▪ EM—subepithelial IC humps |
| Rapidly progressive (crescentic) glomerulonephritis | Poor prognosis, rapidly deteriorating renal function (days to weeks).<br>▪ LM—crescent moon shape C. Crescents consist of fibrin and plasma proteins (eg, C3b) with glomerular parietal cells, monocytes, macrophages<br>Several disease processes may result in this pattern which may be delineated via IF pattern.<br>▪ Linear IF due to antibodies to GBM and alveolar basement membrane: Goodpasture syndrome—hematuria/hemoptysis; type II hypersensitivity reaction. Treatment: plasmapheresis<br>▪ Negative IF/Pauci-immune (no Ig/C3 deposition): granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)—PR3-ANCA/c-ANCA, eosinophilic granulomatosis with polyangiitis or Microscopic polyangiitis—MPO-ANCA/p-ANCA<br>▪ Granular IF—PSGN or DPGN |
| Diffuse proliferative glomerulonephritis | Often due to SLE (think “wire lupus”). DPGN and MPGN often present as nephrotic syndrome and nephritic syndrome concurrently.<br>▪ LM—“wire looping” of capillaries D<br>▪ IF—granular; EM—subendothelial, sometimes subepithelial or intramembranous IgG-based ICs often with C3 deposition |
| IgA nephropathy (Berger disease) | Episodic hematuria that usually occurs concurrently with respiratory or GI tract infections (IgA is secreted by mucosal linings). Renal pathology of IgA vasculitis (HSP).<br>▪ LM—mesangial proliferation<br>▪ IF—IgA-based IC deposits in mesangium; EM—mesangial IC deposition |
| Alport syndrome | Mutation in type IV collagen → irregular thinning and thickening and splitting of glomerular basement membrane.<br>Most commonly X-linked dominant. Eye problems (eg, retinopathy, anterior lenticonus), glomerulonephritis, sensorineural deafness; “can’t see, can’t pee, can’t hear a bee.”<br>▪ EM—“basket-weave” appearance due to irregular thickening of GBM |
| Membrano-proliferative glomerulonephritis | MPGN is a nephritic syndrome that often co-presents with nephrotic syndrome.<br>Type I may be 2° to hepatitis B or C infection. May also be idiopathic.<br>▪ Subendothelial IC deposits with granular IF<br>Type II is associated with C3 nephritic factor (IgG autoantibody that stabilizes C3 convertase → persistent complement activation → ↓ C3 levels).<br>▪ Intramembranous deposits, also called dense deposit disease<br>Both types: mesangial ingrowth → GBM splitting → “tram-track” on H&E and PAS E stains. |



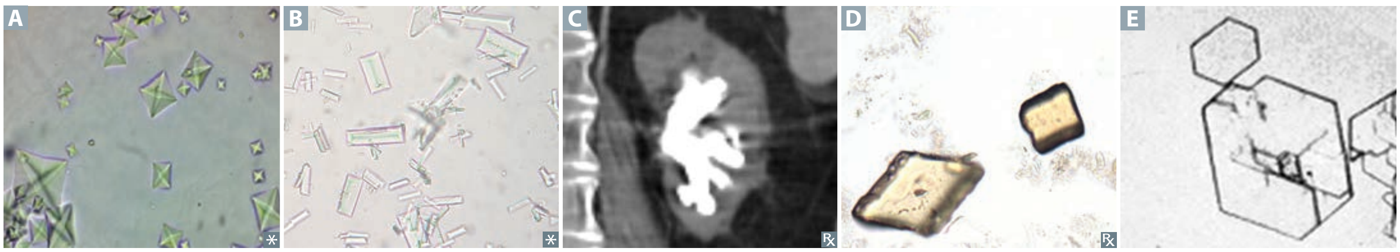
| | |
|---|---|
| **Nephrotic syndrome** | Nephrotic syndrome—massive proteinuria (> 3.5 g/day) |
| **Minimal change disease** | Also known as lipoid nephrosis. Most common cause of nephrotic syndrome in children.<br>Often 1° (idiopathic) and may be triggered by recent infection, immunization, immune stimulus (4 I's of MCD). Rarely, may be 2° to lymphoma (eg, cytokine-mediated damage).<br>1° disease has excellent response to corticosteroids.<br>▪ LM—Normal glomeruli (lipid may be seen in PCT cells)<br>▪ IF—⊖<br>▪ EM—effacement of podocyte foot processes A |
| **Focal segmental glomerulosclerosis** | Higher prevalence in Black people.<br>Can be 1° (idiopathic) or 2° to other conditions (eg, HIV infection, sickle cell disease, heroin use, obesity, interferon treatment, or congenital malformations).<br>1° disease has inconsistent response to steroids. May progress to CKD.<br>▪ LM—segmental sclerosis and hyalinosis B<br>▪ IF—often ⊖ but may be ⊕ for nonspecific focal deposits of IgM, C3, C1<br>▪ EM—effacement of foot processes similar to minimal change disease |
| **Membranous nephropathy** | Also known as membranous glomerulonephritis.<br>Can be 1° (eg, antibodies to phospholipase $A_2$ receptor) or 2° to drugs (eg, NSAIDs, penicillamine, gold), infections (eg, HBV, HCV, syphilis), SLE, or solid tumors.<br>1° disease has poor response to steroids. May progress to CKD.<br>▪ LM—diffuse capillary and GBM thickening C<br>▪ IF—granular due to immune complex (IC) deposition<br>▪ EM—"Spike and dome" appearance of subepithelial deposits |
| **Amyloidosis** | Kidney is the most commonly involved organ (systemic amyloidosis). Associated with chronic conditions that predispose to amyloid deposition (eg, AL amyloid, AA amyloid, prolonged dialysis).<br>▪ LM—Congo red stain shows apple-green birefringence under polarized light due to amyloid deposition in the mesangium |
| **Diabetic glomerulonephropathy** | Most common cause of ESRD in the United States.<br>Hyperglycemia → nonenzymatic glycation of tissue proteins → mesangial expansion; GBM thickening and ↑ permeability. Hyperfiltration (glomerular HTN and ↑ GFR) → glomerular hypertrophy and glomerular scarring (glomerulosclerosis) → further progression of nephropathy.<br>▪ LM—Mesangial expansion, GBM thickening, eosinophilic nodular glomerulosclerosis (Kimmelstiel-Wilson lesions D) |



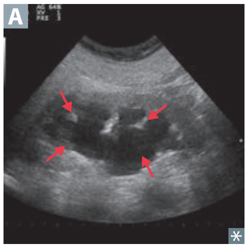
**Kidney stones**

Can lead to severe complications such as hydronephrosis, pyelonephritis, and acute kidney injury. Obstructed stone presents with unilateral flank tenderness, colicky pain radiating to groin, hematuria. Treat and prevent by encouraging fluid intake.

| CONTENT | PRECIPITATES WITH | X-RAY FINDINGS | CT FINDINGS | URINE CRYSTAL | NOTES |
|---|---|---|---|---|---|
| **Calcium** | Calcium oxalate: hypocitraturia | Radiopaque | Radiopaque | Shaped like envelope A or dumbbell | Calcium stones most common (80%); calcium oxalate more common than calcium phosphate stones. Can result from ethylene glycol (antifreeze) ingestion, vitamin C overuse, hypocitraturia (associated with ↓ urine pH), malabsorption (eg, Crohn disease). Treatment: thiazides, citrate, low-sodium diet. |
| | Calcium phosphate: ↑ pH | Radiopaque | Radiopaque | Wedge-shaped prism | Treatment: low-sodium diet, thiazides. |
| **Ammonium magnesium phosphate (struvite)** | ↑ pH | Radiopaque | Radiopaque | Coffin lid B | Account for 15% of stones. Caused by infection with urease ⊕ bugs (eg, *Proteus mirabilis*, *Staphylococcus saprophyticus*, *Klebsiella*) that hydrolyze urea to ammonia → urine alkalinization. Commonly form staghorn calculi C. Treatment: eradication of underlying infection, surgical removal of stone. |
| **Uric acid** | ↓ pH | Radiolucent | Visible | Rhomboid D or rosettes | About 5% of all stones. Risk factors: ↓ urine volume, arid climates, acidic pH. Strong association with hyperuricemia (eg, gout). Often seen in diseases with ↑ cell turnover (eg, leukemia). Treatment: alkalinization of urine, allopurinol. |
| **Cystine** | ↓ pH | Faintly radiopaque | Moderately radiopaque | Hexagonal E | Hereditary (autosomal recessive) condition in which Cystine-reabsorbing PCT transporter loses function, causing cystinuria. Transporter defect also results in poor reabsorption of Ornithine, Lysine, Arginine (COLA). Cystine is poorly soluble, thus stones form in urine. Usually begins in childhood. Can form staghorn calculi. Sodium cyanide nitroprusside test ⊕. "Sixtine" stones have six sides. Treatment: low sodium diet, alkalinization of urine, chelating agents (eg, tiopronin, penicillamine) if refractory. |



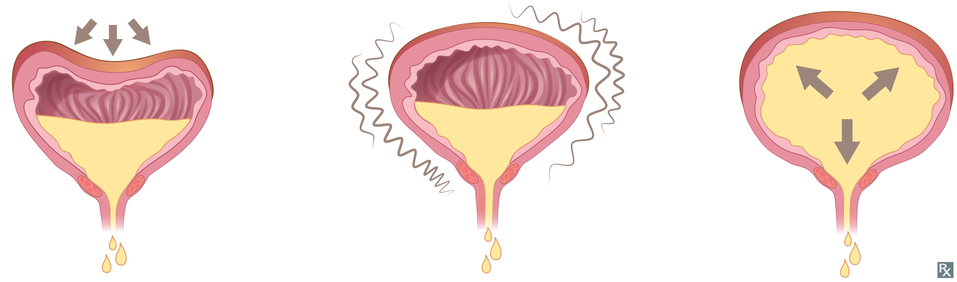
## Hydronephrosis



Distention/dilation of renal pelvis and/or calyces A. Usually caused by urinary tract obstruction (eg, renal stones, severe BPH, congenital obstructions, cervical cancer, injury to ureter); other causes include retroperitoneal fibrosis, vesicoureteral reflux. Dilation occurs proximal to site of pathology. Serum creatinine becomes elevated if obstruction is bilateral or if patient has an obstructed solitary kidney. Leads to compression and possible atrophy of renal cortex and medulla.

## Urinary incontinence

Mixed incontinence has features of both stress and urgency incontinence.



| | Stress incontinence | Urgency incontinence | Overflow incontinence |
|---|---|---|---|
| MECHANISM | Outlet incompetence (urethral hypermobility or intrinsic sphincter deficiency) → leak with ↑ intra-abdominal pressure (eg, sneezing, lifting) ⊕ bladder stress test (directly observed leakage from urethra upon coughing or Valsalva maneuver) | Detrusor overactivity → leak with urge to void immediately | Incomplete emptying (detrusor underactivity or outlet obstruction) → leak with overfilling, ↑ postvoid residual on catheterization or ultrasound |
| ASSOCIATIONS | Obesity, pregnancy, vaginal delivery, prostate surgery | UTI | Polyuria (eg, diabetes), bladder outlet obstruction (eg, BPH), spinal cord injury (eg, MS) |
| TREATMENT | Pelvic floor muscle strengthening (Kegel) exercises, weight loss, pessaries | Kegel exercises, bladder training (timed voiding, distraction or relaxation techniques), antimuscarinics (eg, oxybutynin for overactive bladder), mirabegron | Catheterization, relieve obstruction (eg, $\alpha$-blockers for BPH) |

## Acute cystitis

Inflammation of urinary bladder. Presents as suprapubic pain, dysuria, urinary frequency, urgency. Systemic signs (eg, high fever, chills) are usually absent.

Risk factors include female sex (short urethra), sexual intercourse, indwelling catheter, diabetes mellitus, impaired bladder emptying.

Causes:

- *E coli* (most common)
- *Staphylococcus saprophyticus*—seen in sexually active young women (*E coli* is still more common in this group)
- *Klebsiella*
- *Proteus mirabilis*—urine has ammonia scent

Labs: ⊕ leukocyte esterase. ⊕ nitrites (indicates presence of Enterobacteriaceae). Sterile pyuria (pyuria with ⊖ urine cultures) could suggest urethritis by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.

Treatment: antibiotics (eg, TMP-SMX, nitrofurantoin).

## Pyelonephritis

### Acute pyelonephritis

Neutrophils infiltrate renal interstitium A. Affects cortex with relative sparing of glomeruli/vessels. Presents with fevers, flank pain (costovertebral angle tenderness), nausea/vomiting, chills.

Causes include ascending UTI (*E coli* is most common), hematogenous spread to kidney. Presents with WBCs in urine +/– WBC casts. CT would show striated parenchymal enhancement B.

Risk factors include indwelling urinary catheter, urinary tract obstruction, vesicoureteral reflux, diabetes mellitus, pregnancy.

Complications include chronic pyelonephritis, renal papillary necrosis, perinephric abscess, urosepsis.

Treatment: antibiotics.

### Chronic pyelonephritis

The result of recurrent or inadequately treated episodes of acute pyelonephritis. Typically requires predisposition to infection such as vesicoureteral reflux or chronically obstructing kidney stones.

Coarse, asymmetric corticomedullary scarring, blunted calyces. Tubules can contain eosinophilic casts resembling thyroid tissue C (thyroidization of kidney).

Xanthogranulomatous pyelonephritis—rare; grossly orange nodules that can mimic tumor nodules; characterized by widespread kidney damage due to granulomatous tissue containing foamy macrophages. Associated with *Proteus* infection.

## Acute kidney injury

| | Prerenal azotemia | Intrinsic renal failure | Postrenal azotemia |
|---|---|---|---|
| ETIOLOGY | Hypovolemia<br>↓ cardiac output<br>↓ effective circulating volume (eg, HF, liver failure) | Tubules and interstitium:<br>▪ Acute tubular necrosis (ischemia, nephrotoxins)<br>▪ Acute interstitial nephritis<br>Glomerulus:<br>▪ Acute glomerulonephritis<br>Vascular:<br>▪ Vasculitis<br>▪ Malignant hypertension<br>▪ TTP-HUS | Stones<br>BPH<br>Neoplasm<br>Congenital anomalies |
| PATHOPHYSIOLOGY | ↓ RBF → ↓ GFR → ↑ reabsorption of $Na^+/H_2O$ and urea | In ATN, patchy necrosis → debris obstructing tubules and fluid backflow → ↓ GFR | Outflow obstruction (bilateral) |
| URINE OSMOLALITY (mOsm/kg) | >500 | <350 | <350 |
| URINE $Na^+$ (mEq/L) | <20 | >40 | Varies |
| $FE_{Na}$ | <1% | >2% | Varies |
| SERUM BUN/Cr | >20 | <15 | Varies |

## Acute interstitial nephritis

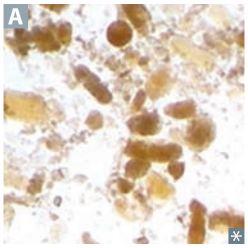
Also called tubulointerstitial nephritis. Acute interstitial renal inflammation. Pyuria (classically eosinophils) and azotemia occurring after administration of drugs that act as haptens, inducing hypersensitivity (eg, diuretics, NSAIDs, penicillin derivatives, proton pump inhibitors, rifampin, quinolones, sulfonamides). Less commonly may be 2° to other processes such as systemic infections (eg, *Mycoplasma*) or autoimmune diseases (eg, Sjögren syndrome, SLE, sarcoidosis).

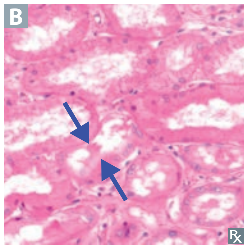
Associated with fever, rash, pyuria, hematuria, and costovertebral angle tenderness, but can be asymptomatic.

Remember these **5 P'S**:

- **P**ee (diuretics)
- **P**ain-free (NSAIDs)
- **P**enicillins and cephalosporins
- **P**roton pump inhibitors
- Rifam**P**in
- **S**ulfa drugs

### Acute tubular necrosis





Most common cause of acute kidney injury in hospitalized patients. Spontaneously resolves in many cases. Can be fatal, especially during initial oliguric phase. ↑ $FE_{Na}$.

Key finding: granular casts (often muddy brown in appearance) A.

3 stages:

1. Inciting event
2. Maintenance phase—oliguric; lasts 1–3 weeks; risk of hyperkalemia, metabolic acidosis, uremia
3. Recovery phase—polyuric; BUN and serum creatinine fall; risk of hypokalemia and renal wasting of other electrolytes and minerals

Can be caused by ischemic or nephrotoxic injury:

- Ischemic—2° to ↓ renal blood flow (eg, hypotension, shock, sepsis, hemorrhage, HF). Results in death of tubular cells that may slough into tubular lumen B (PCT and thick ascending limb are highly susceptible to injury).
- Nephrotoxic—2° to injury resulting from toxic substances (eg, aminoglycosides, radiocontrast agents, lead, cisplatin, ethylene glycol), crush injury (myoglobinuria), hemoglobinuria. Proximal tubules are particularly susceptible to injury.

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### Diffuse cortical necrosis

Acute generalized cortical infarction of both kidneys. Likely due to a combination of vasospasm and DIC.

Associated with obstetric catastrophes (eg, abruptio placentae), septic shock.

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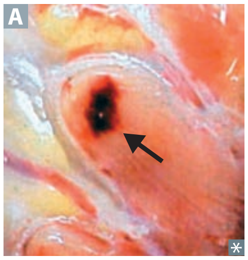
### Renal papillary necrosis



Sloughing of necrotic renal papillae A → gross hematuria. May be triggered by recent infection or immune stimulus.

Associated with:

- **S**ickle cell disease or trait
- **A**cute pyelonephritis
- **A**nalgesics (eg, NSAIDs)
- **D**iabetes mellitus

**SAAD papa** with **pap**illary necrosis.

---

### Consequences of renal failure

Decline in renal filtration can lead to excess retained nitrogenous waste products and electrolyte disturbances.

Consequences (**MAD HUNGER**):

- **M**etabolic **A**cidosis
- **D**yslipidemia (especially ↑ triglycerides)
- **H**igh potassium
- **U**remia
- **N**a$^+$/$H_2O$ retention (HF, pulmonary edema, hypertension)
- **G**rowth retardation and developmental delay
- **E**rythropoietin deficiency (anemia)
- **R**enal osteodystrophy

2 forms of renal failure: acute (eg, ATN) and chronic (eg, hypertension, diabetes mellitus, congenital anomalies).

Incremental reductions in GFR define the stages of chronic kidney disease.

Normal phosphate levels are maintained during early stages of CKD due to ↑ levels of fibroblast growth factor 23 (FGF23), which promotes renal excretion of phosphate.

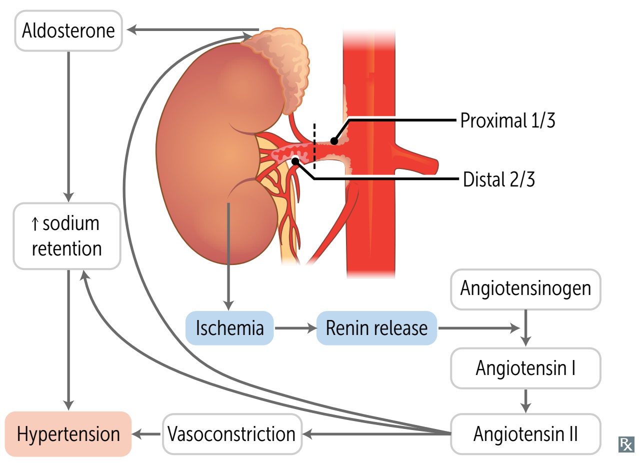
Uremia—syndrome resulting from high serum urea. Can present with nausea, anorexia, encephalopathy (seen with asterixis), pericarditis, platelet dysfunction. Management: dialysis.

| | |
|---|---|
| **Renal osteodystrophy** | Hypocalcemia, hyperphosphatemia, and failure of vitamin D hydroxylation associated with chronic kidney disease → 2° hyperparathyroidism → 3° hyperparathyroidism (if 2° poorly managed). High serum phosphate can bind with $Ca^{2+}$ → tissue deposits → ↓ serum $Ca^{2+}$. ↓ 1,25-$(OH)_2D_3$ → ↓ intestinal $Ca^{2+}$ absorption. Causes subperiosteal thinning of bones. |

## Renal cyst disorders

| | |
|---|---|
| **Autosomal dominant polycystic kidney disease** | Numerous cysts in cortex and medulla A causing bilateral enlarged kidneys ultimately destroy kidney parenchyma. Presents with combinations of flank pain, hematuria, hypertension, urinary infection, progressive renal failure in ~ 50% of individuals.<br>Mutation in *PKD1* (85% of cases, chromosome 16) or *PKD2* (15% of cases, chromosome 4). Complications include chronic kidney disease and hypertension (caused by ↑ renin production). Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts, diverticulosis.<br>Treatment: If hypertension or proteinuria develops, treat with ACE inhibitors or ARBs. |
| **Autosomal recessive polycystic kidney disease** | Cystic dilation of collecting ducts B. Often presents in infancy. Associated with congenital hepatic fibrosis. Significant oliguric renal failure in utero can lead to Potter sequence. Concerns beyond neonatal period include systemic hypertension, progressive renal insufficiency, and portal hypertension from congenital hepatic fibrosis. |
| **Autosomal dominant tubulointerstitial kidney disease** | Also called medullary cystic kidney disease. Causes tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; smaller kidneys on ultrasound. Poor prognosis. |
| **Simple vs complex renal cysts** | Simple cysts are filled with ultrafiltrate (anechoic on ultrasound C). Very common and account for majority of all renal masses. Found incidentally and typically asymptomatic.<br>Complex cysts, including those that are septated, enhanced, or have solid components on imaging require follow-up or removal due to possibility of renal cell carcinoma. |

## Renovascular disease




Unilateral or bilateral renal artery stenosis (RAS) → ↓ renal perfusion → ↑ renin → ↑ angiotensin → HTN. Most common cause of 2° HTN in adults.

Main causes of RAS:
- Atherosclerotic plaques: proximal 1/3 of renal artery, usually in older males, smokers.
- Fibromuscular dysplasia: distal 2/3 of renal artery or segmental branches, usually young or middle-aged females

For unilateral RAS, affected kidney can atrophy → asymmetric kidney size. Renal venous sampling will show ↑ renin in affected kidney, ↓ renin in unaffected kidney.

For bilateral RAS, patients can have a sudden rise in creatinine after starting an ACE inhibitor, ARB, or renin inhibitor, due to their interference on RAAS-mediated renal perfusion.

Can present with severe/refractory HTN, flash pulmonary edema, epigastric/flank bruit. Patients with RAS may also have stenosis in other large vessels.

## Renal cell carcinoma

Polygonal clear cells **A** filled with accumulated lipids and carbohydrate. Often golden-yellow **B** due to ↑ lipid content.

Originates from PCT → invades renal vein (may develop varicocele if left sided) → IVC → hematogenous spread → metastasis to lung and bone.

Manifests with hematuria, palpable masses, 2° polycythemia, flank pain, fever, weight loss.

Treatment: surgery/ablation for localized disease. Immunotherapy (eg, ipilimumab) or targeted therapy for metastatic disease, rarely curative. Resistant to chemotherapy and radiation therapy.

Class triad: flank pain, palpable mass, hematuria.

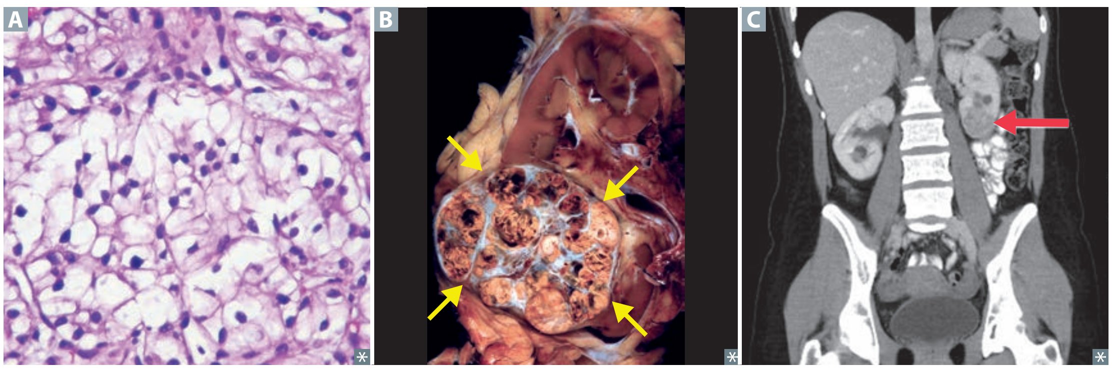
Most common 1° renal malignancy **C**.

Most common in males 50–70 years old, ↑ incidence with tobacco smoking and obesity.

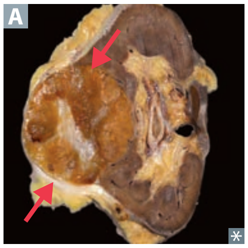
Associated with paraneoplastic syndromes, eg, **P**THrP, **E**ctopic EPO, **A**CTH, **R**enin ("**PEAR**"-aneoplastic).

Clear cell (most common subtype) associated with gene deletion on chromosome 3 (sporadic, or inherited as von Hippel-Lindau syndrome).

**RCC** = **3** letters = chromosome **3** = associated with **VHL** (also 3 letters).



## Renal oncocytoma

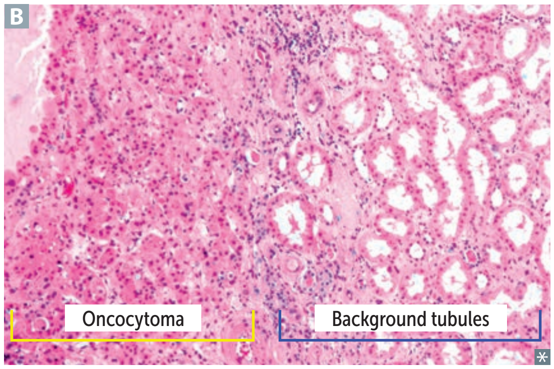



Benign epithelial cell tumor arising from collecting ducts (arrows in A point to well-circumscribed mass with central scar).

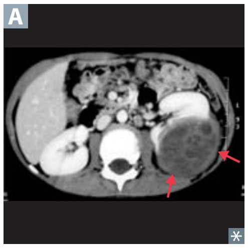
Large eosinophilic cells with abundant mitochondria without perinuclear clearing B (vs chromophobe renal cell carcinoma).

Presents with painless hematuria, flank pain, abdominal mass.

Often resected to exclude malignancy (eg, renal cell carcinoma).




## Nephroblastoma



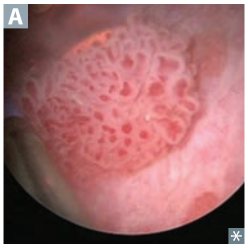

Also called Wilms tumor. Most common renal malignancy of early childhood (ages 2–4). Contains embryonic glomerular structures. Most often present with large, palpable, unilateral flank mass A and/or hematuria and possible HTN.

Can be associated with loss-of-function mutations of tumor suppressor genes *WT1* or *WT2* on chromosome 11.

May be a part of several syndromes:

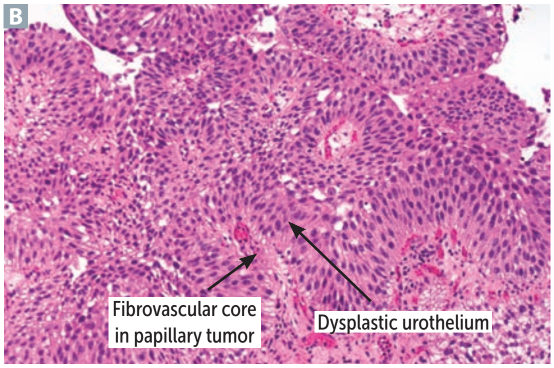
- **WAGR complex**—**W**ilms tumor, **A**niridia (absence of iris), **G**enitourinary malformations, **R**ange of developmental delays (*WT1* deletion)
- **Denys-Drash syndrome**—Wilms tumor, **D**iffuse mesangial sclerosis (early-onset nephrotic syndrome), **D**ysgenesis of gonads (male pseudohermaphroditism), *WT1* mutation
- **Beckwith-Wiedemann syndrome**—**W**ilms tumor, macroglossia, organomegaly, hemihyperplasia (***W****T2* mutation), omphalocele

## Urothelial carcinoma of the bladder




Also called transitional cell carcinoma. Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder) A B. Can be suggested by painless hematuria (no casts).

Associated with problems in your **P**ee **SAC**: **P**henacetin, tobacco **S**moking, **A**romatic amines (found in dyes), **C**yclophosphamide.



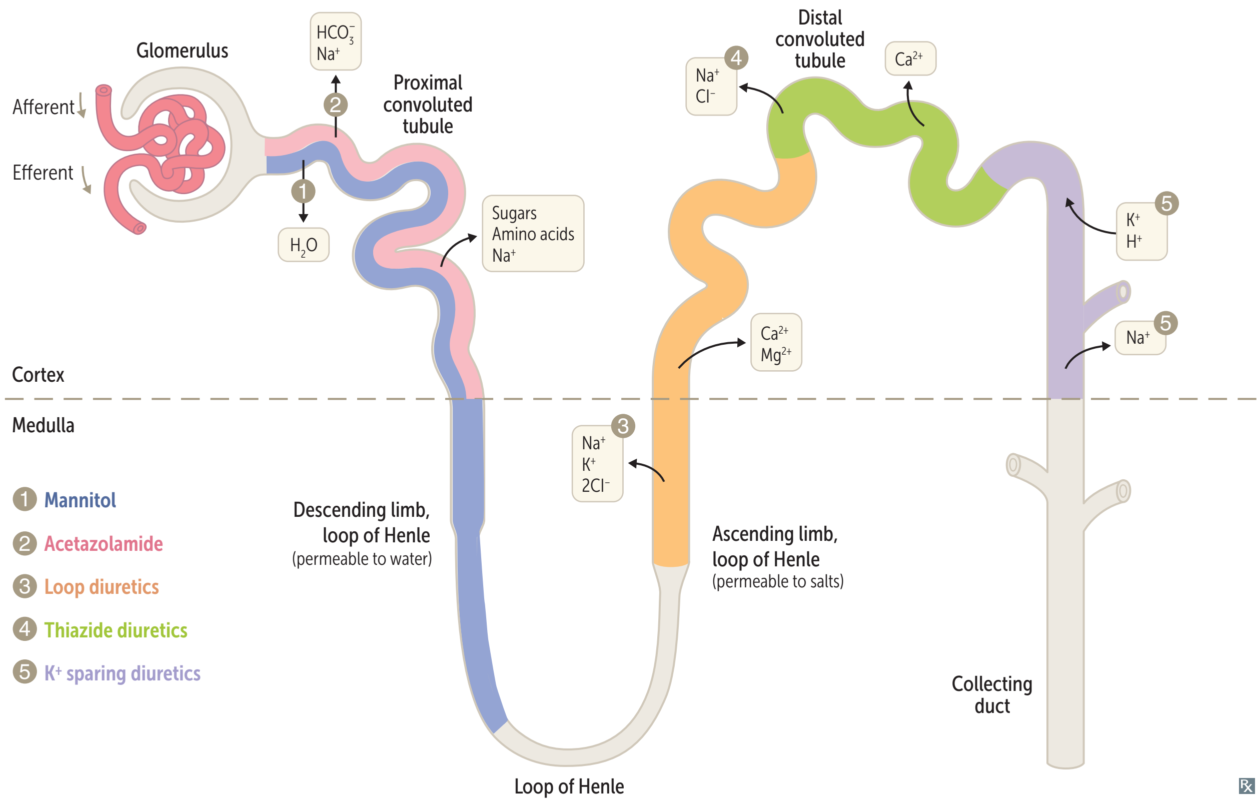

## Squamous cell carcinoma of the bladder

Chronic irritation of urinary bladder → squamous metaplasia → dysplasia and squamous cell carcinoma.

Risk factors include **4 S**'s: ***S****chistosoma haematobium* infection (Middle East), chronic cystitis ("**s**ystitis"), **smoking, chronic nephrolithiasis** (**s**tones). Presents with painless hematuria (no casts).

## ▸ RENAL—PHARMACOLOGY

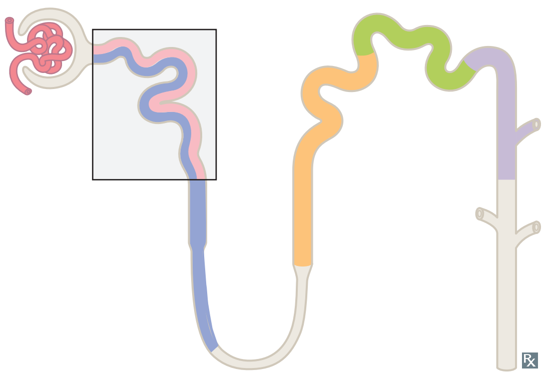
### Diuretics site of action




### Mannitol

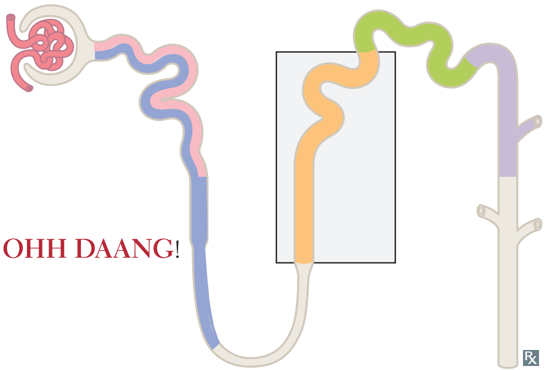
| | |
|---|---|
| MECHANISM | Osmotic diuretic. ↑ tubular fluid osmolarity → ↑ urine flow, ↓ intracranial/intraocular pressure. |
| CLINICAL USE | Drug overdose, elevated intracranial/intraocular pressure. |
| ADVERSE EFFECTS | Dehydration, hypo- or hypernatremia, pulmonary edema. Contraindicated in anuria, HF. |

## Acetazolamide

| | | |
|---|---|---|
| MECHANISM | Carbonic anhydrase inhibitor. Causes self-limited $NaHCO_3$ diuresis and ↓ total body $HCO_3^-$ stores. Alkalinizes urine. |  |
| CLINICAL USE | Glaucoma, metabolic alkalosis, altitude sickness (by offsetting respiratory alkalosis), idiopathic intracranial hypertension. | |
| ADVERSE EFFECTS | Proximal renal tubular acidosis (type 2 RTA), paresthesias, $NH_3$ toxicity, sulfa allergy, hypokalemia. Promotes calcium phosphate stone formation (insoluble at high pH). | "**Acid**"azolamide causes **acid**osis. |

## Loop diuretics

### Furosemide, bumetanide, torsemide

| | | |
|---|---|---|
| MECHANISM | Sulfonamide loop diuretics. Inhibit cotransport system ($Na^+/K^+/2Cl^-$) of thick ascending limb of loop of Henle. Abolish hypertonicity of medulla, preventing concentration of urine. Associated with ↑ PGE (vasodilatory effect on afferent arteriole); inhibited by NSAIDs. ↑ $Ca^{2+}$ excretion. **L**oops **l**ose $Ca^{2+}$. |  |
| CLINICAL USE | Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia. | |
| ADVERSE EFFECTS | **O**totoxicity, **H**ypokalemia, **H**ypomagnesemia, **D**ehydration, **A**llergy (sulfa), metabolic **A**lkalosis, **N**ephritis (interstitial), **G**out. | **OHH DAANG**! |

### Ethacrynic acid

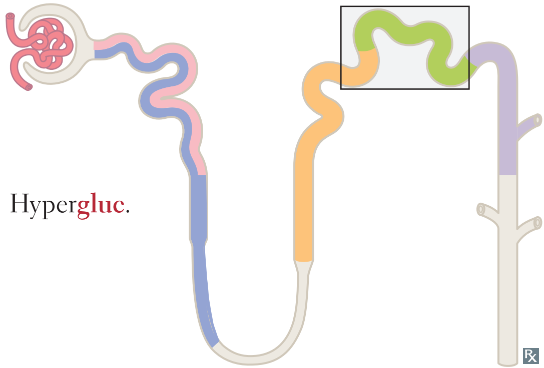
| | | |
|---|---|---|
| MECHANISM | Nonsulfonamide inhibitor of cotransport system ($Na^+/K^+/2Cl^-$) of thick ascending limb of **loop** of Henle. | |
| CLINICAL USE | Diuresis in patients allergic to sulfa drugs. | |
| ADVERSE EFFECTS | Similar to furosemide, but more **oto**toxic. | **Loop** earrings hurt your **ears**. |

## Thiazide diuretics

Hydrochlorothiazide, chlorthalidone, metolazone.

| | |
|---|---|
| MECHANISM | Inhibit NaCl reabsorption in early DCT → ↓ diluting capacity of nephron. ↓ $Ca^{2+}$ excretion. |
| CLINICAL USE | Hypertension, HF, idiopathic hypercalciuria, nephrogenic diabetes insipidus, osteoporosis. |
| ADVERSE EFFECTS | Hypokalemic metabolic alkalosis, hyponatremia, hyper**g**lycemia, hyper**l**ipidemia, hyper**u**ricemia, hyper**c**alcemia. Sulfa allergy. |

Hyper**gluc**.

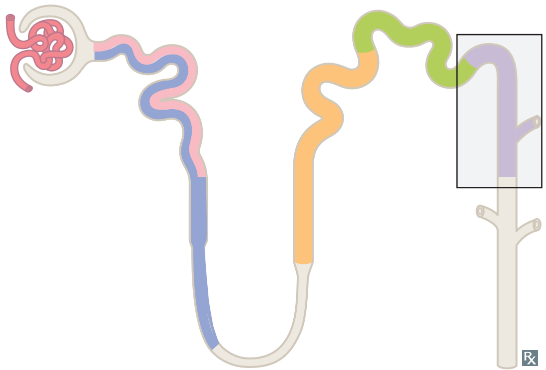


## Potassium-sparing diuretics

**S**pironolactone, **E**plerenone, **A**miloride, **T**riamterene.

**K**eep your **SEAT**.

| | |
|---|---|
| MECHANISM | Spironolact**one** and epleren**one** are competitive aldoster**one** receptor antagonists in cortical collecting tubule. Triamterene and amiloride block $Na^+$ channels at the same part of the tubule. |
| CLINICAL USE | Hyperaldosteronism, $K^+$ depletion, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride), antiandrogen (spironolactone). |
| ADVERSE EFFECTS | Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (eg, gynecomastia, antiandrogen effects). |



## Diuretics: electrolyte changes

| | |
|---|---|
| **Urine NaCl** | ↑ with all diuretics (concentration varies based on potency of diuretic effect). Serum NaCl may decrease as a result. |
| **Urine $K^+$** | ↑ especially with loop and thiazide diuretics, excluding $K^+$-sparing diuretics. |
| **Blood pH** | ↓ (**acidemia**): carbonic anhydrase inhibitors: ↓ $HCO_3^-$ reabsorption. $K^+$ sparing: aldosterone blockade prevents $K^+$ secretion and $H^+$ secretion. Additionally, hyperkalemia leads to $K^+$ entering all cells (via $H^+/K^+$ exchanger) in exchange for $H^+$ exiting cells.<br>↑ (**alkalemia**): loop diuretics and thiazides cause alkalemia through several mechanisms:<br>▪ Volume contraction → ↑ AT II → ↑ $Na^+/H^+$ exchange in PCT → ↑ $HCO_3^-$ reabsorption ("contraction alkalosis")<br>▪ $K^+$ loss leads to $K^+$ exiting all cells (via $H^+/K^+$ exchanger) in exchange for $H^+$ entering cells<br>▪ In low $K^+$ state, $H^+$ (rather than $K^+$) is exchanged for $Na^+$ in cortical collecting tubule → alkalosis and "paradoxical aciduria" |
| **Urine $Ca^{2+}$** | ↑ with loop diuretics: ↓ paracellular $Ca^{2+}$ reabsorption → hypocalcemia.<br>↓ with thiazides: enhanced $Ca^{2+}$ reabsorption. |

| **Angiotensin-converting enzyme inhibitors** | Captopril, enalapril, lisinopril, ramipril. | |
|---|---|---|
| MECHANISM | Inhibit ACE → ↓ AT II → ↓ GFR by preventing constriction of efferent arterioles. ↑ renin due to loss of negative feedback. Inhibition of ACE also prevents inactivation of bradykinin, a potent vasodilator. | |
| CLINICAL USE | Hypertension, HF (↓ mortality), proteinuria, diabetic nephropathy. Prevent unfavorable heart remodeling as a result of chronic hypertension. | In chronic kidney disease (eg, diabetic nephropathy), ↓ intraglomerular pressure, slowing GBM thickening. |
| ADVERSE EFFECTS | **C**ough, **A**ngioedema (both due to ↑ bradykinin; contraindicated in C1 esterase inhibitor deficiency), **T**eratogen (fetal renal malformations), ↑ **C**reatinine (↓ GFR), **H**yperkalemia, and **H**ypotension. Used with caution in bilateral renal artery stenosis because ACE inhibitors will further ↓ GFR → renal failure. | Captopril's **CATCHH**. |

| **Angiotensin II receptor blockers** | Losartan, candesartan, valsartan. |
|---|---|
| MECHANISM | Selectively block binding of angiotensin II to $AT_1$ receptor. Effects similar to ACE inhibitors, but ARBs do not increase bradykinin. |
| CLINICAL USE | Hypertension, HF, proteinuria, or chronic kidney disease (eg, diabetic nephropathy) with intolerance to ACE inhibitors (eg, cough, angioedema). |
| ADVERSE EFFECTS | Hyperkalemia, ↓ GFR, hypotension; teratogen. |

| **Aliskiren** | |
|---|---|
| MECHANISM | Direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I. Alis**kiren ki**lls **ren**in. |
| CLINICAL USE | Hypertension. |
| ADVERSE EFFECTS | Hyperkalemia, ↓ GFR, hypotension, angioedema. Relatively contraindicated in patients already taking ACE inhibitors or ARBs and contraindicated in pregnancy. |

▶ NOTES

# Reproductive

*"Life is always a rich and steady time when you are waiting for something to happen or to hatch."*

—E.B. White, *Charlotte's Web*

*"Love is only a dirty trick played on us to achieve continuation of the species."*

—W. Somerset Maugham

*"In pregnancy, there are two bodies, one inside the other. Two people live under one skin. When so much of life is dedicated to maintaining our integrity as distinct beings, this bodily tandem is an uncanny fact."*

—Joan Raphael-Leff, *Pregnancy: The Inside Story*

*"Life is a sexually transmitted disease and the mortality rate is one hundred percent."*

—R.D. Laing



Organizing the reproductive system by key concepts such as embryology, endocrinology, pregnancy, and oncology can help with understanding this complex topic. Study the endocrine and reproductive chapters together, because mastery of the hypothalamic-pituitary-gonadal axis is key to answering questions on ovulation, menstruation, disorders of sexual development, contraception, and many pathologies.

Embryology is a nuanced subject that spans multiple organ systems. Approach it from a clinical perspective. For instance, make the connection between the presentation of DiGeorge syndrome and the 3rd/4th pharyngeal pouch, and between the Müllerian/Wolffian systems and disorders of sexual development.

As for oncology, don't worry about remembering screening or treatment guidelines. It is more important to recognize the clinical presentation (eg, signs and symptoms) of reproductive cancers and their associated labs, histopathology, and risk factors. In addition, some of the testicular and ovarian cancers have distinct patterns of hCG, AFP, LH, or FSH derangements that serve as helpful clues in exam questions.

## ▶ REPRODUCTIVE—EMBRYOLOGY

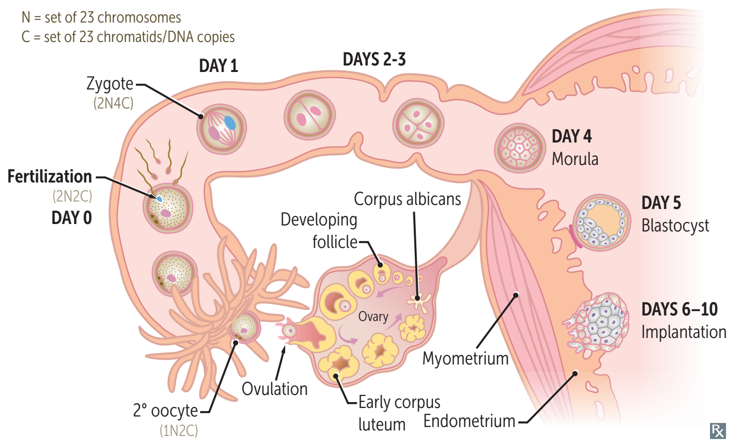
### Important genes of embryogenesis

| GENE | LOCATION | FUNCTION | NOTES |
|---|---|---|---|
| **Sonic hedgehog (*SHH*) gene** | Zone of polarizing activity at base of limb buds | Anterior-posterior axis patterning, CNS development | Mutations → holoprosencephaly |
| ***Wnt*-7 gene** | Apical ectodermal ridge at distal end of each limb | Dorsal-ventral axis patterning, limb development | "*Vnt*-7" |
| **Fibroblast growth factor (*FGF*) gene** | Apical ectodermal ridge | Limb lengthening (via mitosis of mesoderm) | "Look at that Fetus, Growing Fingers" |
| **Homeobox (*Hox*) genes** | Multiple | Segmental organization in cranial-caudal direction, transcription factor coding | Mutations → appendages in wrong locations. Isotretinoin → ↑ *Hox* gene expression |

### Early fetal development

Timeline shown is based on developmental age (ie, time since fertilization) rather than gestational age (ie, time since first day of last menstrual period).

**Early embryonic development**




| | | |
|---|---|---|
| **Within week 1** | hCG secretion begins around the time of implantation of blastocyst. | Blastocyst "sticks" at day 6. |
| **Within week 2** | Bilaminar disc (epiblast, hypoblast). | 2 weeks = 2 layers. |
| **Within week 3** | Gastrulation forms trilaminar embryonic disc. Cells from epiblast invaginate → primitive streak → endoderm, mesoderm, ectoderm. Notochord arises from midline mesoderm and induces overlying ectoderm to become neural plate. | 3 weeks = 3 layers. |
| **Weeks 3–8 (embryonic period)** | Neural tube formed by neuroectoderm and closes by week 4.<br>Organogenesis. | Extremely susceptible to teratogens. |
| **Week 4** | Heart begins to beat. Cardiac activity visible by transvaginal ultrasound.<br>Upper and lower limb buds begin to form. | 4 weeks = 4 limbs and 4 heart chambers. |
| **Week 6** | Fetal movements start. | |
| **Week 8** | Genitalia have male/female characteristics. | |

## Embryologic derivatives

| | | |
|---|---|---|
| **Ectoderm** | | External/outer layer |
| Surface ectoderm | Epidermis; adenohypophysis (from Rathke pouch); lens of eye; epithelial linings of oral cavity, sensory organs of ear, and olfactory epithelium; anal canal below the pectinate line; parotid, sweat, mammary glands. | Craniopharyngioma—benign Rathke pouch tumor with cholesterol crystals, calcifications. |
| Neural tube | Brain (neurohypophysis, CNS neurons, oligodendrocytes, astrocytes, ependymal cells, pineal gland), retina, spinal cord. | Neuroectoderm—think CNS. |
| Neural crest | **E**nterochromaffin cells, **L**eptomeninges (arachnoid, pia), **M**elanocytes, **O**dontoblasts, **P**NS ganglia (cranial, dorsal root, autonomic), **A**drenal medulla, **S**chwann cells, **S**piral membrane (aorticopulmonary septum), **E**ndocardial cushions (also derived partially from mesoderm), **S**kull bones. | **ELMO PASSES**<br>Neural crest—think PNS and non-neural structures nearby. |
| **Mesoderm** | Muscle, bone, connective tissue, serous linings of body cavities (eg, peritoneum, pericardium, pleura), spleen (develops within foregut mesentery), cardiovascular structures, lymphatics, blood, wall of gut tube, upper 2/3 of vagina, kidneys, adrenal cortex, dermis, testes, ovaries, microglia, dura mater, tracheal cartilage.<br>Notochord induces ectoderm to form neuroectoderm (neural plate); its only postnatal derivative is the nucleus pulposus of the intervertebral disc. | **M**iddle/"**m**eat" layer.<br>Mesodermal defects = **VACTERL** association:<br>**V**ertebral defects<br>**A**nal atresia<br>**C**ardiac defects<br>**T**racheo-**E**sophageal fistula<br>**R**enal defects<br>**L**imb defects (bone and muscle) |
| **Endoderm** | Gut tube epithelium (including anal canal above the pectinate line), most of urethra and lower 1/3 of vagina (derived from urogenital sinus), luminal epithelial derivatives (eg, lungs, liver, gallbladder, pancreas, eustachian tube, thymus, parathyroid, thyroid follicular and parafollicular [C] cells). | "**En**ternal" layer. |

## Types of errors in morphogenesis

| | |
|---|---|
| **Agenesis** | Absent organ due to absent primordial tissue. |
| **Aplasia** | Absent organ despite presence of primordial tissue. |
| **Hypoplasia** | Incomplete organ development; primordial tissue present. |
| **Disruption** | 2° breakdown of previously normal tissue or structure (eg, amniotic band syndrome). |
| **Deformation** | Extrinsic mechanical distortion (eg, congenital torticollis); occurs after embryonic period. |
| **Malformation** | Intrinsic developmental defect; occurs during embryonic period (weeks 3–8 of development). |
| **Sequence** | Abnormalities result from a single 1° embryologic event (eg, oligohydramnios → Potter sequence). |
| **Field defect** | Disturbance of tissues that develop in a contiguous physical space (eg, holoprosencephaly). |

**Teratogens**

Most susceptible in 3rd–8th weeks (embryonic period—organogenesis) of development. Before week 3, "all-or-none" effects. After week 8, growth and function affected.

| TERATOGEN | EFFECTS ON FETUS | NOTES |
|---|---|---|
| **Medications** | | |
| **ACE inhibitors** | Renal failure, oligohydramnios, hypocalvaria | |
| **Alkylating agents** | Absence of digits, multiple anomalies | |
| **Aminoglycosides** | Ototoxicity | A mean guy hit the baby in the ear |
| **Antiepileptic drugs** | Neural tube defects, cardiac defects, cleft palate, skeletal abnormalities (eg, phalanx/nail hypoplasia, facial dysmorphism) | High-dose folate supplementation recommended; most commonly valproate, carbamazepine, phenytoin, phenobarbital |
| **Diethylstilbestrol** | Vaginal clear cell adenocarcinoma, congenital Müllerian anomalies | |
| **Fluoroquinolones** | Cartilage damage | |
| **Folate antagonists** | Neural tube defects | Antiepileptics, trimethoprim, methotrexate |
| **Isotretinoin** | Craniofacial (eg, microtia, dysmorphism), CNS, cardiac, and thymic defects | Contraception mandatory. Pronounce "isoteratinoin." |
| **Lithium** | Ebstein anomaly | |
| **Methimazole** | Aplasia cutis congenita (congenital absence of skin, particularly on scalp) | |
| **Tetracyclines** | Discolored teeth, inhibited bone growth | "Teethracyclines" |
| **Thalidomide** | Limb defects (phocomelia, micromelia—"flipper" limbs) | Limb defects with "tha-limb-domide" |
| **Warfarin** | Bone and cartilage deformities (stippled epiphyses, nasal and limb hypoplasia), optic nerve atrophy, fetal cerebral hemorrhage | Do not wage warfare on the baby; keep it heppy with heparin (does not cross placenta) |
| **Substance use** | | |
| **Alcohol** | Fetal alcohol syndrome | |
| **Cocaine** | Low birth weight, preterm birth, IUGR, placental abruption | Cocaine → vasoconstriction |
| **Smoking** | Low birth weight (leading cause in developed countries), preterm labor, placental problems, IUGR, SIDS, ADHD | Nicotine → vasoconstriction<br>CO → impaired $O_2$ delivery |
| **Other** | | |
| **Iodine lack or excess** | Congenital hypothyroidism (cretinism), congenital goiter | |
| **Diabetes in pregnancy** | Caudal regression syndrome, cardiac defects (eg, VSD), neural tube defects, macrosomia, neonatal hypoglycemia (due to islet cell hyperplasia), polycythemia, neonatal respiratory distress syndrome | |
| **Methylmercury** | Neurotoxicity | Higher concentrations in top-predator fish (eg, shark, swordfish, king mackerel, tilefish) |
| **X-rays** | Microcephaly, intellectual disability | Minimized by lead shielding |

**Fetal alcohol syndrome**

One of the leading preventable causes of intellectual disability in the US. Newborns of patients who consumed alcohol during any stage of pregnancy have ↑ incidence of congenital abnormalities, including pre- and postnatal developmental delay, microcephaly, facial abnormalities A (eg, smooth philtrum, thin vermillion border, small palpebral fissures), limb dislocation, heart defects. Heart-lung fistulas and holoprosencephaly may occur in more severe presentations. One mechanism is due to impaired migration of neuronal and glial cells.

**Neonatal abstinence syndrome**

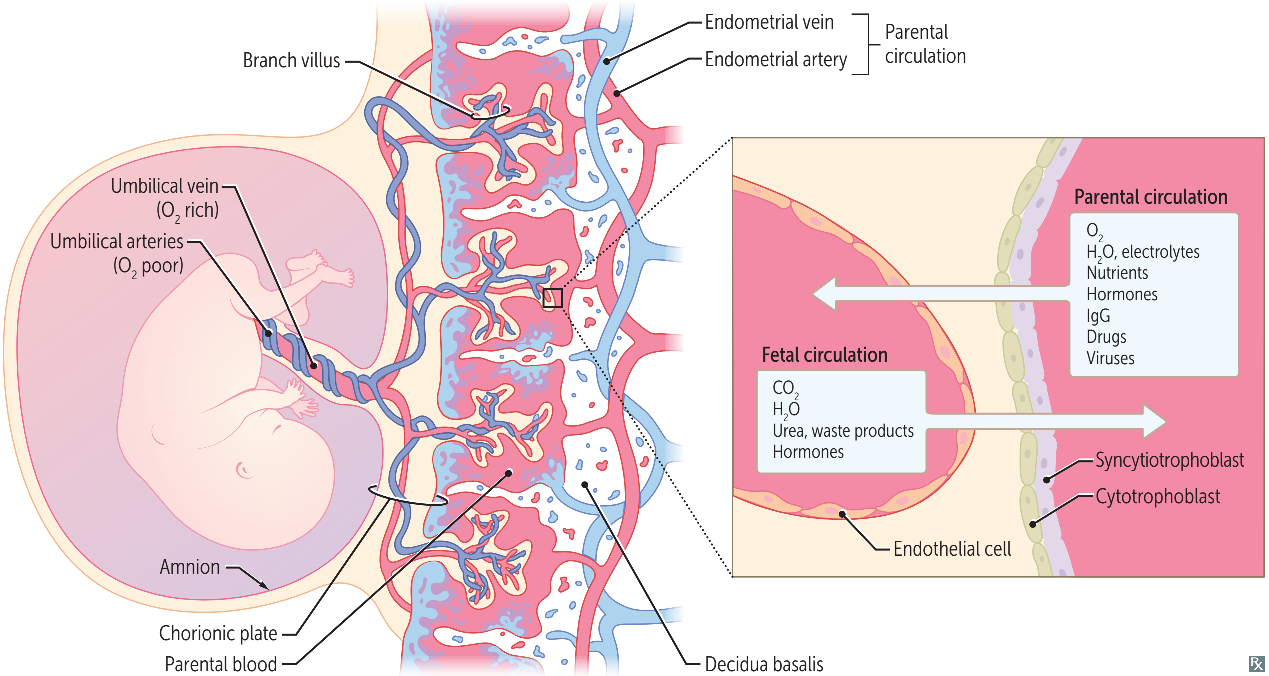
Complex disorder involving CNS, ANS, and GI systems. Secondary to substance use (most commonly opioids) during pregnancy.

Universal screening for substance use is recommended in all pregnant patients.

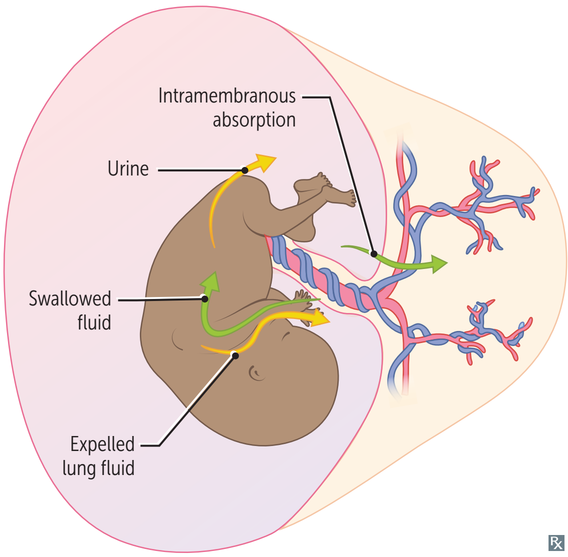
Newborns may present with uncoordinated sucking reflexes, irritability, high-pitched crying, tremors, tachypnea, sneezing, diarrhea, and possibly seizures.

Treatment (for opiate use): methadone, morphine, buprenorphine.

| | |
|---|---|
| **Placenta** | 1° site of nutrient and gas exchange between pregnant patient and fetus. |
| **Fetal component** | |
| **Cytotrophoblast** | Inner layer of chorionic villi; makes **c**ells. |
| **Syncytiotrophoblast** | Outer layer of chorionic villi; **syn**thesizes and secretes hormones, eg, hCG (structurally similar to LH; stimulates corpus luteum to secrete progesterone during first trimester). Lacks MHC I expression → ↓ chance of attack by maternal immune system. |
| **Parental component** | |
| **Decidua basalis** | Derived from endometrium. Parental blood in lacunae. |




## Amniotic fluid




Derived from fetal urine (mainly) and fetal lung liquid.

Cleared by fetal swallowing (mainly) and intramembranous absorption.

**Polyhydramnios**—too much amniotic fluid. May be idiopathic or associated with fetal malformations (eg, esophageal/duodenal atresia, anencephaly; both result in inability to swallow amniotic fluid), diabetes in pregnant patient, fetal anemia, multiple gestations.

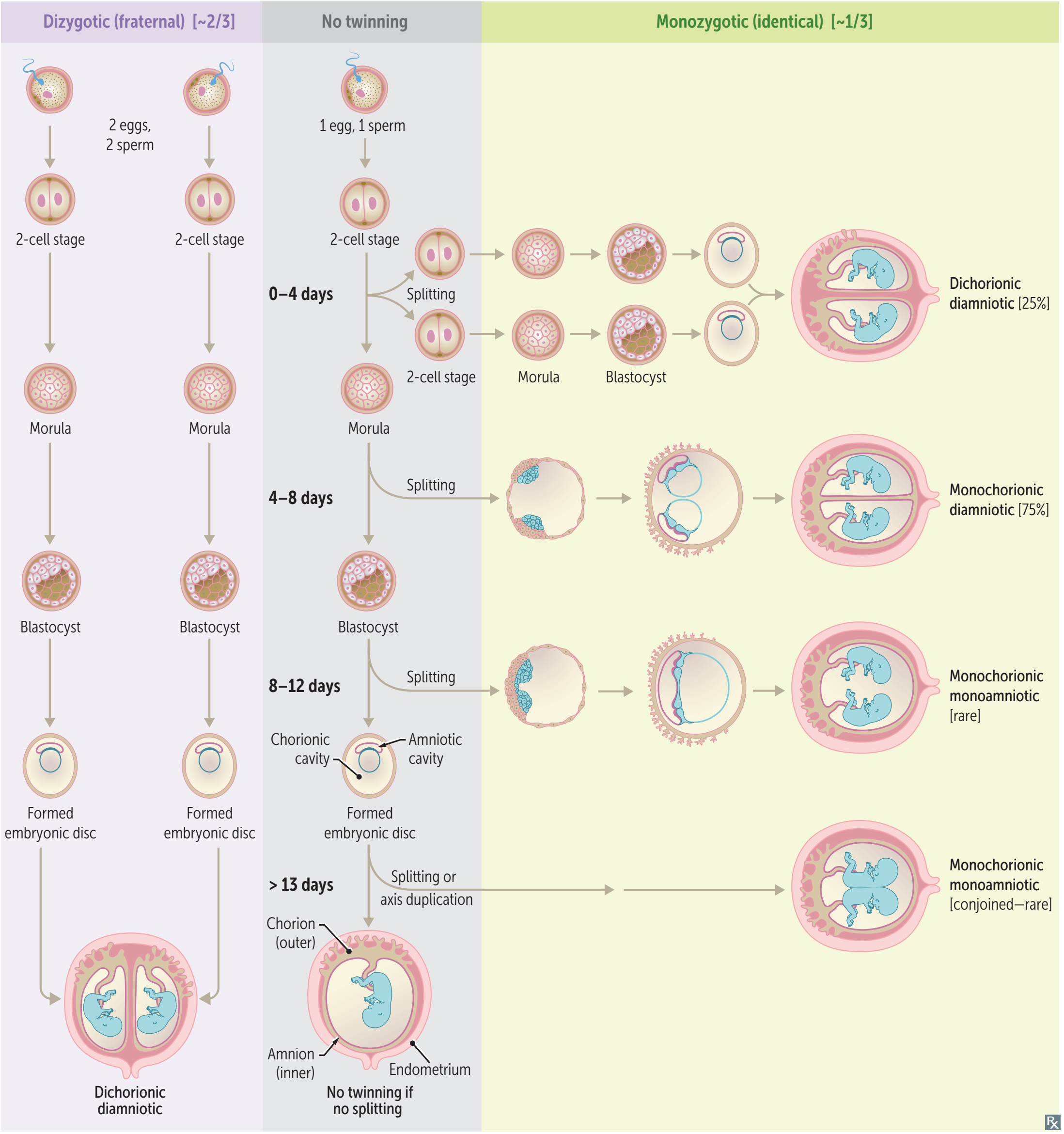
**Oligohydramnios**—too little amniotic fluid. Associated with placental insufficiency, bilateral renal agenesis, posterior urethral valves (in males); these result in inability to excrete urine. Profound oligohydramnios can cause Potter sequence.

**Twinning**

Dizygotic ("fraternal") twins arise from 2 eggs that are separately fertilized by 2 different sperm (always 2 zygotes) and will have 2 separate amniotic sacs and 2 separate placentas (chorions).

Monozygotic ("identical") twins arise from 1 fertilized egg (1 egg + 1 sperm) that splits in early pregnancy. The timing of splitting determines chorionicity (number of chorions) and amnionicity (number of amnions) (take **separate** cars or **share** a **CCAB**):

- Splitting 0–4 days: **separate** chorion and amnion (di-di)
- Splitting 4–8 days: **shared C**horion (mo-di)
- Splitting 8–12 days: **shared C**horion and **A**mnion (mo-mo)
- Splitting 13+ days: **shared B**ody (conjoined)

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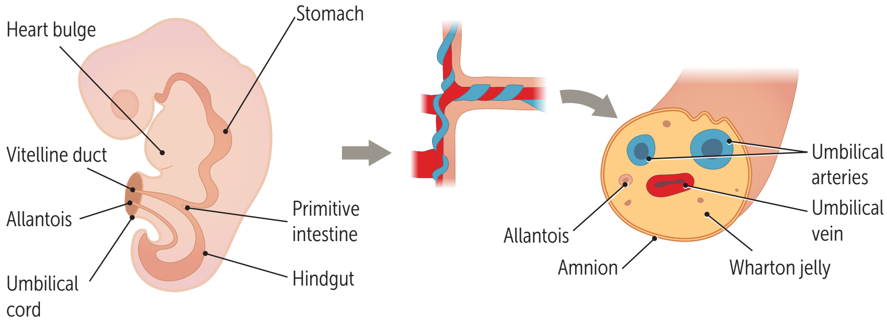
**Twin-twin transfusion syndrome**

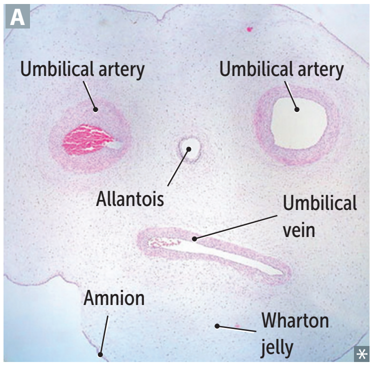
Occurs in monochorionic twin gestations. Unbalanced vascular connections between twins in shared placenta → net blood flow from one twin to the other.

Donor twin → hypovolemia and oligohydramnios ("stuck twin" appearance).

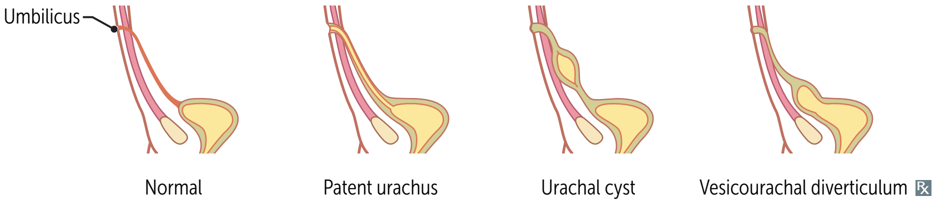
Recipient twin → hypervolemia and polyhydramnios.

| | | |
|---|---|---|
| **Umbilical cord** | Two umbilical arteries return deoxygenated blood from fetal internal iliac arteries to placenta A.<br>One umbilical vein supplies oxygenated blood from placenta to fetus; drains into IVC via liver or via ductus venosus. | Single umbilical artery (2-vessel cord) is associated with congenital and chromosomal anomalies.<br>Umbilical arteries and vein are derived from allantois. |

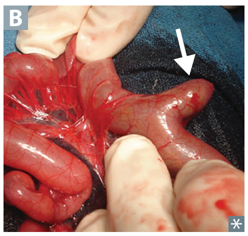


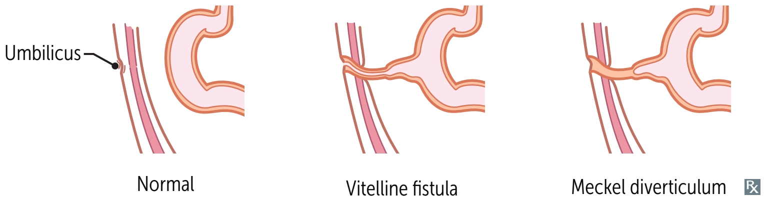




| | |
|---|---|
| **Urachus** | Allantois forms from hindgut and extends into urogenital sinus. Allantois becomes the urachus, a duct between fetal bladder and umbilicus. Failure of urachus to involute can lead to anomalies that may increase risk of infection and/or malignancy (eg, adenocarcinoma) if not treated.<br>Obliterated urachus is represented by the median umbilical ligament after birth, which is covered by median umbilical fold of the peritoneum. |
| Patent urachus | Total failure of urachus to obliterate → urine discharge from umbilicus. |
| Urachal cyst | Partial failure of urachus to obliterate; fluid-filled cavity lined with uroepithelium, between umbilicus and bladder. Cyst can become infected and present as painful mass below umbilicus. |
| Vesicourachal diverticulum | Slight failure of urachus to obliterate → outpouching of bladder. |




| | |
|---|---|
| **Vitelline duct** | Also called omphalomesenteric duct. Connects yolk sac to midgut lumen. Obliterates during week 7 of development. |
| Patent vitelline duct | Total failure of vitelline duct to obliterate → meconium discharge from umbilicus. |
| Vitelline duct cyst | Partial failure of vitelline duct to obliterate. ↑ risk for volvulus. |
| Meckel diverticulum | Slight failure of vitelline duct to obliterate → outpouching of ileum (true diverticulum, arrow in B). Usually asymptomatic. May have heterotopic gastric and/or pancreatic tissue → melena, hematochezia, abdominal pain. |

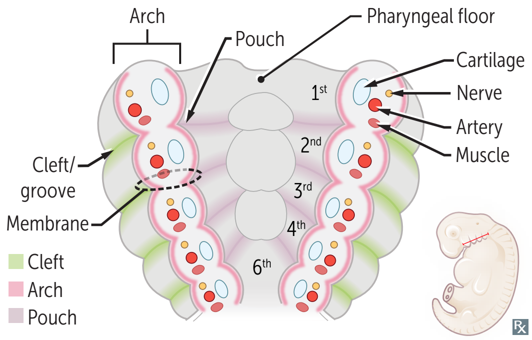


**Pharyngeal apparatus**

Composed of pharyngeal (branchial) clefts, arches, pouches.
Pharyngeal clefts—derived from ectoderm. Also called pharyngeal grooves.
Pharyngeal arches—derived from mesoderm (muscles, arteries) and neural crest (bones, cartilage).
Pharyngeal pouches—derived from endoderm.

CAP covers outside to inside:
Clefts = ectoderm
Arches = mesoderm + neural crest
Pouches = endoderm

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**Pharyngeal cleft derivatives**

1st cleft develops into external auditory meatus.
2nd through 4th clefts form temporary cervical sinuses, which are obliterated by proliferation of 2nd arch mesenchyme.
Pharyngeal cleft cyst—persistent cervical sinus; presents as lateral neck mass anterior to sternocleidomastoid muscle that does not move with swallowing (vs thyroglossal duct cyst).

**Pharyngeal arch derivatives**

When at the restaurant of the golden **arches**, children tend to first **chew** (1), then **smile** (2), then **swallow stylishly** (3) or **simply swallow** (4), and then **speak** (6).

| ARCH | CARTILAGE | MUSCLES | NERVES[a] | NOTES |
|---|---|---|---|---|
| **1st pharyngeal arch** | Maxillary process → maxilla, zygomatic bone<br>Mandibular process → meckel cartilage → mandible, malleus and incus, sphenomandibular ligament | Muscles of mastication (temporalis, masseter, lateral and medial pterygoids), mylohyoid, anterior belly of digastric, tensor tympani, anterior 2/3 of tongue, tensor veli palatini | CN $V_3$ **chew** | Pierre Robin sequence—micrognathia, glossoptosis, cleft palate, airway obstruction<br>Treacher Collins syndrome—autosomal dominant neural crest dysfunction → craniofacial abnormalities (eg, zygomatic bone and mandibular hypoplasia), hearing loss, airway compromise |
| **2nd pharyngeal arch** | Reichert cartilage: stapes, styloid process, lesser horn of hyoid, stylohyoid ligament | Muscles of facial expression, stapedius, stylohyoid, platysma, posterior belly of digastric | CN VII (seven) **smile** (facial expression) | |
| **3rd pharyngeal arch** | Greater horn of hyoid | Stylopharyngeus | CN IX (stylo-pharyngeus) **swallow stylishly** | |
| **4th and 6th pharyngeal arches** | Arytenoids, Cricoid, Corniculate, Cuneiform, Thyroid (used to sing and ACCCT) | 4th arch: most pharyngeal constrictors; cricothyroid, levator veli palatini<br>6th arch: all intrinsic muscles of larynx except cricothyroid | 4th arch: CN X (superior laryngeal branch) **simply swallow**<br>6th arch: CN X (recurrent/inferior laryngeal branch) **speak** | Arches 3 and 4 form posterior 1/3 of tongue<br>Arch 5 makes no major developmental contributions |

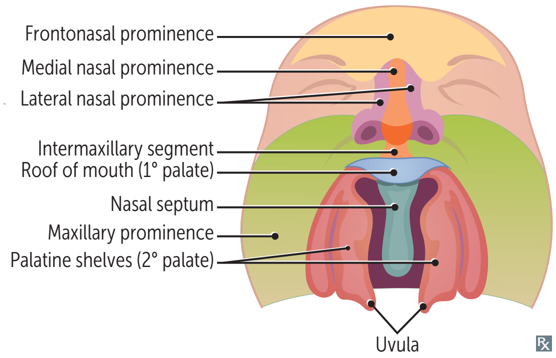
[a]Sensory and motor nerves are not pharyngeal arch derivatives. They grow into the arches and are derived from neural crest (sensory) and neuroectoderm (motor).

**Pharyngeal pouch derivatives**

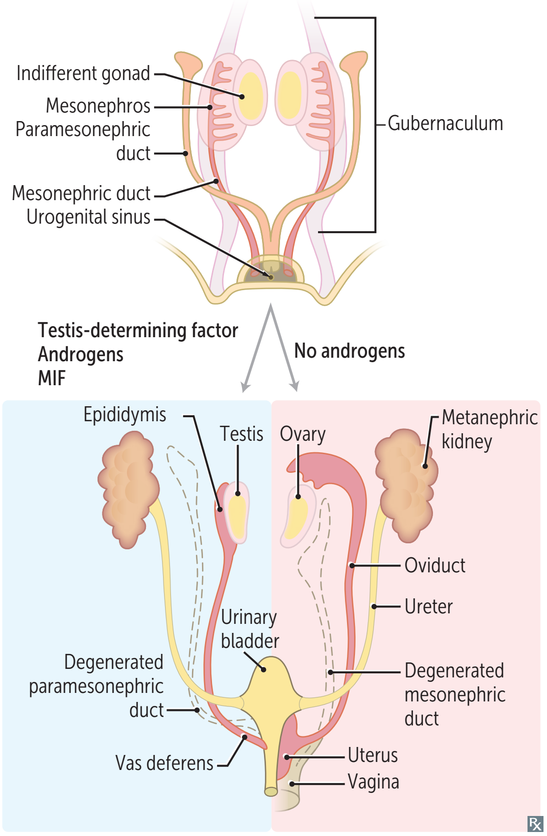
**Ear, tonsils, bottom-to-top**: 1 (**ear**), 2 (**tonsils**), 3 dorsal (**bottom** for inferior parathyroids), 3 ventral (**to** = **thymus**), 4 (**top** = **superior** parathyroids)

| POUCH | DERIVATIVES | NOTES |
|---|---|---|
| **1st pharyngeal pouch** | Middle ear cavity, eustachian tube, mastoid air cells | 1st pouch contributes to endoderm-lined structures of ear |
| **2nd pharyngeal pouch** | Epithelial lining of palatine tonsil | |
| **3rd pharyngeal pouch** | Dorsal wings → **inferior** parathyroids<br>Ventral wings → thymus | Third pouch contributes to thymus and both inferior parathyroids<br>Structures from 3rd pouch end up **below** those from 4th pouch |
| **4th pharyngeal pouch** | Dorsal wings → **superior** parathyroids<br>Ventral wings → ultimopharyngeal body → parafollicular (C) cells of thyroid | 4th pharyngeal pouch forms para"4"llicular cells |

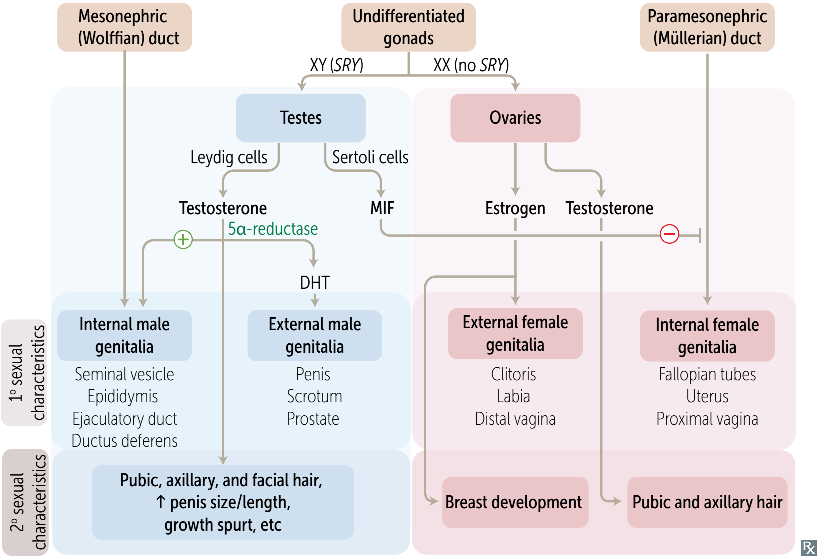
| **Orofacial clefts** | Cleft lip and cleft palate have distinct, multifactorial etiologies, but often occur together. |
| --- | --- |
| **Cleft lip** | Due to failure of fusion of the maxillary and merged medial nasal processes (formation of 1° palate). |
| **Cleft palate** | Due to failure of fusion of the two lateral palatine shelves or failure of fusion of lateral palatine shelf with the nasal septum and/or 1° palate (formation of 2° palate). |




| **Genital embryology** | |
| --- | --- |
| **Female** | Default development. Mesonephric duct degenerates and paramesonephric duct develops. |
| **Male** | *SRY* gene on Y chromosome—produces testis-determining factor → testes development.<br>Sertoli cells secrete Müllerian inhibitory factor (MIF, also called antimullerian hormone) that suppresses development of paramesonephric ducts.<br>Leydig cells secrete androgens that stimulate development of mesonephric ducts. |
| **Paramesonephric (Müllerian) duct** | Develops into female internal structures—fallopian tubes, uterus, upper portion of vagina (lower portion from urogenital sinus). Male remnant is appendix testis.<br>Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome)—may present as 1° amenorrhea (due to a lack of uterine development) in females with fully developed 2° sexual characteristics (functional ovaries). |
| **Mesonephric (Wolffian) duct** | Develops into male internal structures (except prostate)—**S**eminal vesicles, **E**pididymis, **E**jaculatory duct, **D**uctus deferens (**SEED**).<br>Female remnant is Gartner duct. |



## Sexual differentiation



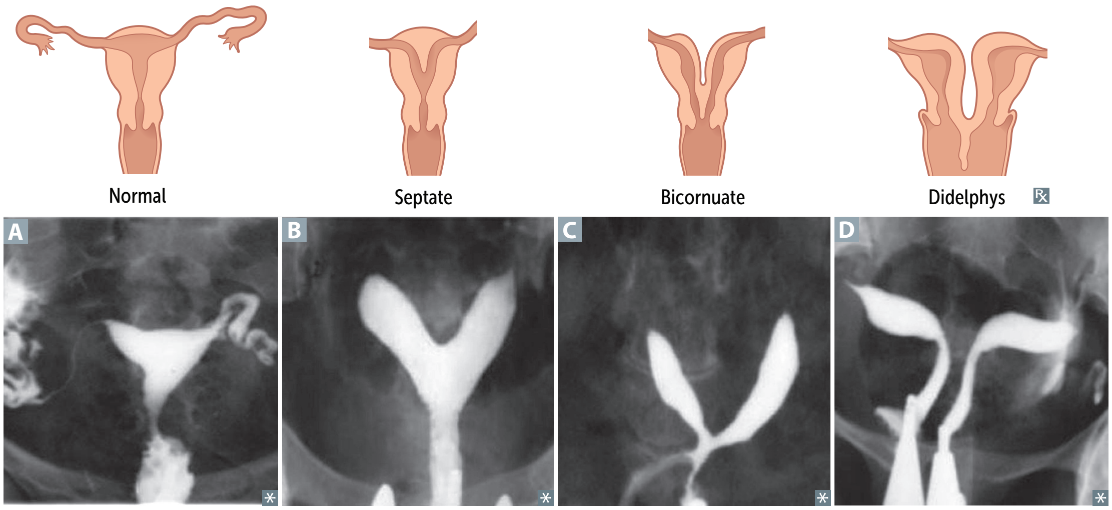

Absence of Sertoli cells or lack of Müllerian inhibitory factor → develop both male and female internal genitalia and male external genitalia (streak gonads)

5α-reductase deficiency—inability to convert testosterone into DHT → male internal genitalia, ambiguous external genitalia until puberty (when ↑ testosterone levels cause masculinization)

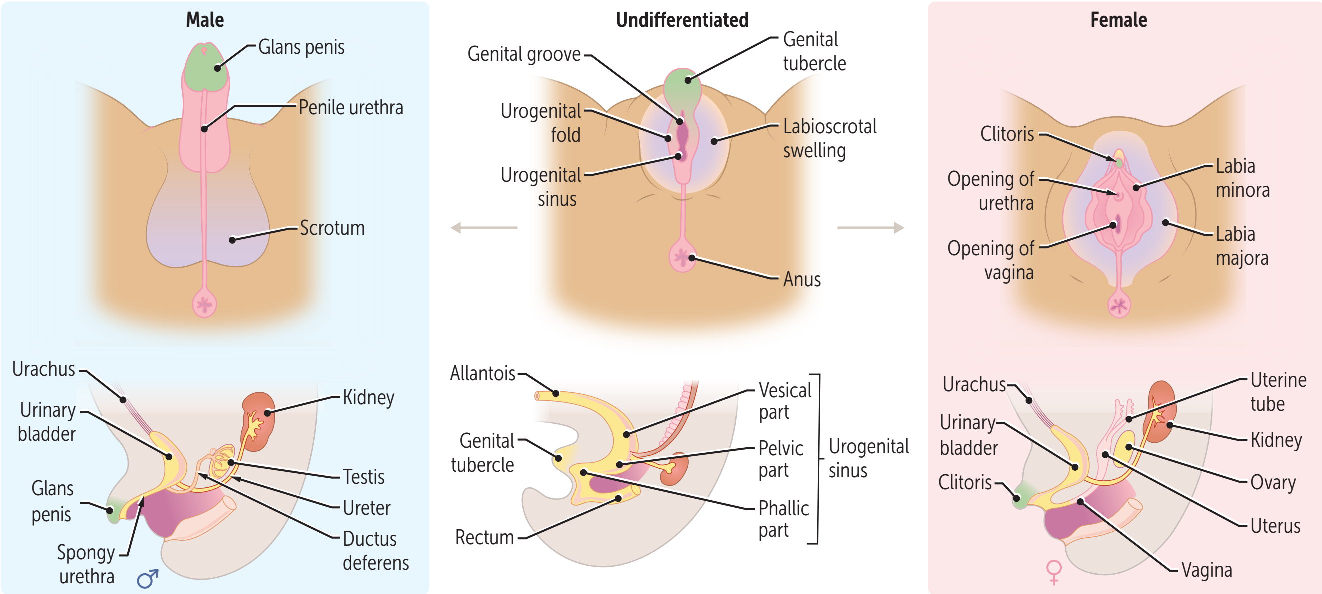
In the testes:

- Leydig leads to male (internal and external) sexual differentiation.
- Sertoli shuts down female (internal) sexual differentiation.

| | |
|---|---|
| **Uterine (Müllerian duct) anomalies** | ↓ fertility and ↑ risk of complicated pregnancy (eg, spontaneous abortion, prematurity, IUGR, malpresentation). Contrast with normal uterus A. |
| **Septate uterus** | Incomplete resorption of septum B. Common anomaly. Treat with septoplasty. |
| **Bicornuate uterus** | Incomplete fusion of Müllerian ducts C. |
| **Uterus didelphys** | Complete failure of fusion → double uterus, cervix, vagina D. |



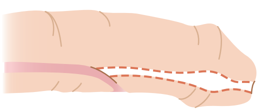
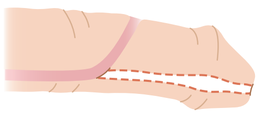
## Male/female genital homologs




| Dihydrotestosterone (male) | Precursor | Estrogen (female) |
|---|---|---|
| Glans penis | Genital tubercle | Glans clitoris |
| Corpus cavernosum and spongiosum | Genital tubercle | Vestibular bulbs |
| Bulbourethral glands (of Cowper) | Urogenital sinus | Greater vestibular glands (of Bartholin) |
| Prostate gland | Urogenital sinus | Urethral and paraurethral glands (of Skene) |
| Ventral shaft of penis (penile urethra) | Urogenital folds | Labia minora |
| Scrotum | Labioscrotal swelling | Labia majora |

℞

## Congenital penile abnormalities

| | | |
|---|---|---|
| **Hypospadias**  ℞ | Abnormal opening of penile urethra on ventral (under) surface due to failure of urethral folds to fuse. | Hypospadias is more common than epispadias. Associated with inguinal hernia, cryptorchidism, chordee (downward or upward bending of penis). Can be seen in 5α-reductase deficiency. |
| **Epispadias**  ℞ | Abnormal opening of penile urethra on dorsal (top) surface due to faulty positioning of genital tubercle. | Exstrophy of the bladder is associated with epispadias. |

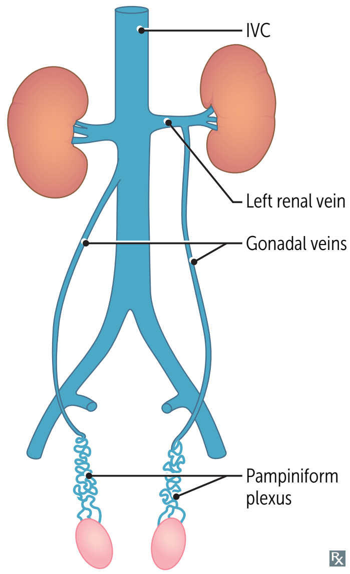
## Descent of testes and ovaries

| | DESCRIPTION | MALE REMNANT | FEMALE REMNANT |
|---|---|---|---|
| **Gubernaculum** | Band of fibrous tissue | Anchors testes within scrotum | Ovarian ligament + round ligament of uterus |
| **Processus vaginalis** | Evagination of peritoneum | Forms tunica vaginalis<br>Persistent patent processus vaginalis → hydrocele | Obliterated |

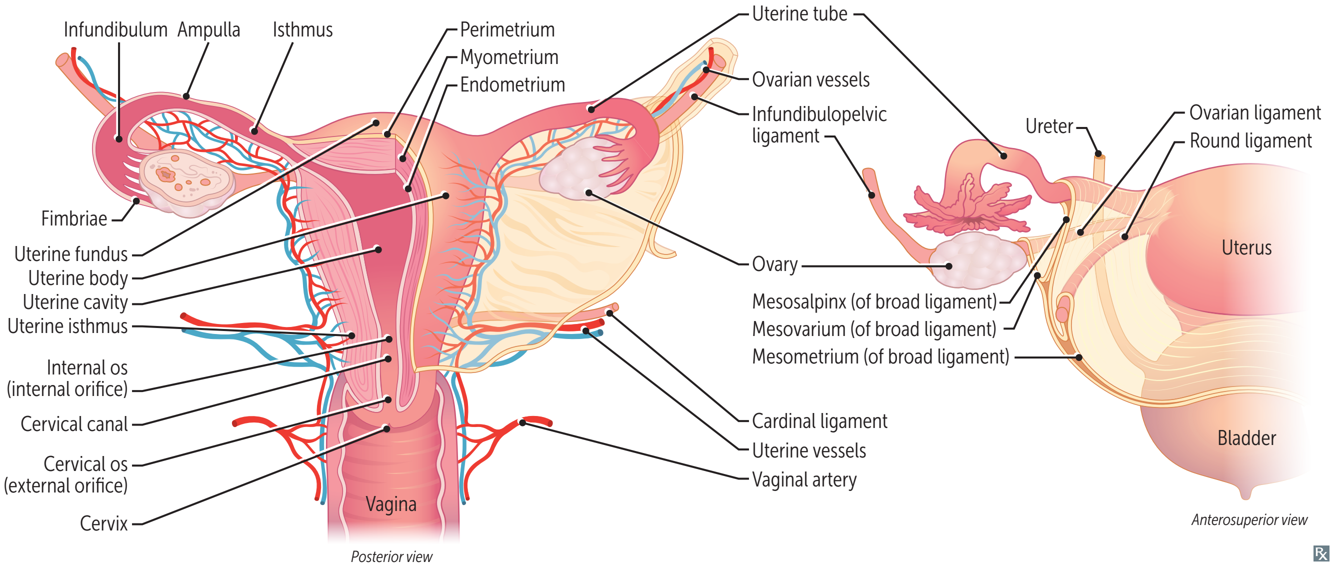
# ▸ REPRODUCTIVE—ANATOMY

## Gonadal drainage

| | | |
|---|---|---|
| **Venous drainage** | Left ovary/testis → left gonadal vein → left renal vein → IVC.<br>Right ovary/testis → right gonadal vein → IVC.<br>Because the left spermatic vein enters the left renal vein at a 90° angle, flow is less laminar on left than on right → left venous pressure > right venous pressure → varicocele more common on the left. | "Left gonadal vein takes the longer way." |
| **Lymphatic drainage** | Ovaries/testes/fundus of uterus → para-aortic lymph nodes.<br>Body of uterus/cervix/superior part of bladder → external iliac nodes.<br>Prostate/cervix/corpus cavernosum/proximal vagina → internal iliac nodes.<br>Distal vagina/vulva/scrotum/distal anus → superficial inguinal nodes.<br>Clitoris/glans penis → deep inguinal nodes. | |



### Female reproductive anatomy




| LIGAMENT | CONNECTS | STRUCTURES CONTAINED | NOTES |
|---|---|---|---|
| **Infundibulopelvic (suspensory) ligament** | Ovaries to lateral pelvic wall | Ovarian vessels | Ureter courses retroperitoneally, close to gonadal vessels → ligation of ovarian vessels during oophorectomy presents risk to ureter |
| **Cardinal (transverse cervical) ligament** | Cervix to side wall of pelvis | Uterine vessels | Ligation of uterine vessels during hysterectomy presents risk to ureter |
| **Round ligament of the uterus** | Uterine horn to labia majora | | Derivative of gubernaculum. Travels through round inguinal canal; above the artery of Sampson |
| **Broad ligament** | Uterus, fallopian tubes, and ovaries to pelvic side wall | Ovaries, fallopian tubes, round ligaments of uterus | Fold of peritoneum that comprises the mesosalpinx, mesometrium, and mesovarium |
| **Ovarian ligament** | Medial pole of ovary to uterine horn | | Derivative of gubernaculum<br>Ovarian ligament latches to lateral uterus |

**Adnexal torsion**

Twisting of ovary and fallopian tube around infundibulopelvic ligament and ovarian ligament → compression of ovarian vessels in infundibulopelvic ligament → blockage of lymphatic and venous outflow. Continued arterial perfusion → ovarian edema → complete blockage of arterial inflow → necrosis, local hemorrhage. Associated with ovarian masses. Presents with acute pelvic pain, adnexal mass, nausea/vomiting. Surgical emergency.

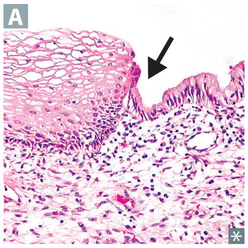
**Pelvic organ prolapse**

Herniation of pelvic organs to or beyond the vaginal walls (anterior, posterior) or apex. Associated with multiparity, ↑ age, obesity. Presents with pelvic pressure, tissue protrusion from vagina, urinary frequency, constipation, sexual dysfunction.

- Anterior compartment prolapse—bladder (cystocele). Most common.
- Posterior compartment prolapse—rectum (rectocele) or small bowel (enterocele).
- Apical compartment prolapse—uterus, cervix, or vaginal vault.

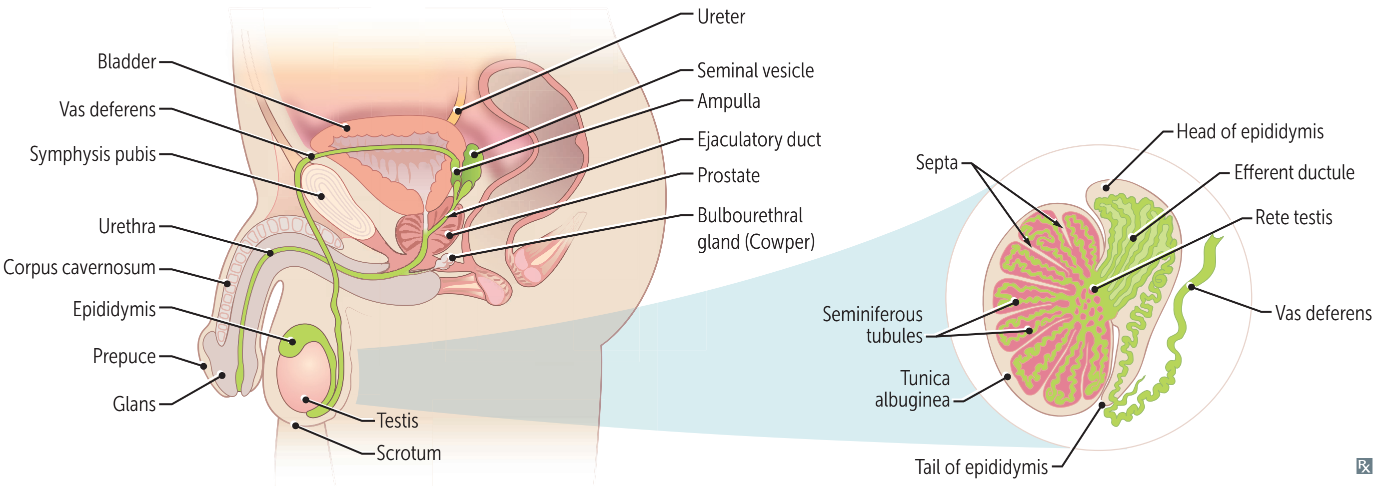
Uterine procidentia—herniation involving all 3 compartments.

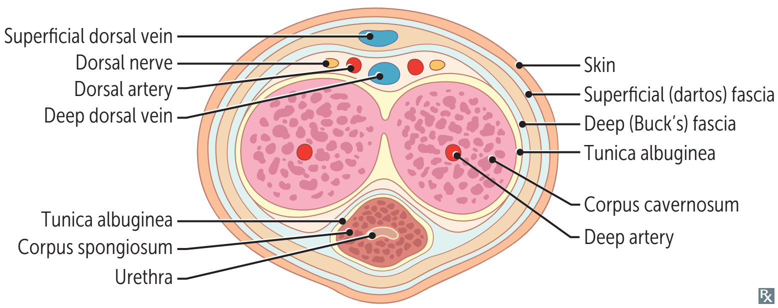
## Female reproductive epithelial histology




| TISSUE | HISTOLOGY/NOTES |
| --- | --- |
| Vulva | Stratified squamous epithelium |
| Vagina | Stratified squamous epithelium, nonkeratinized |
| Ectocervix | Stratified squamous epithelium, nonkeratinized |
| Transformation zone | Squamocolumnar junction A (most common area for cervical cancer; sampled in Pap test) |
| Endocervix | Simple columnar epithelium |
| Uterus | Simple columnar epithelium with long tubular glands in proliferative phase; coiled glands in secretory phase |
| Fallopian tube | Simple columnar epithelium, ciliated |
| Ovary, outer surface | Simple cuboidal epithelium (germinal epithelium covering surface of ovary) |

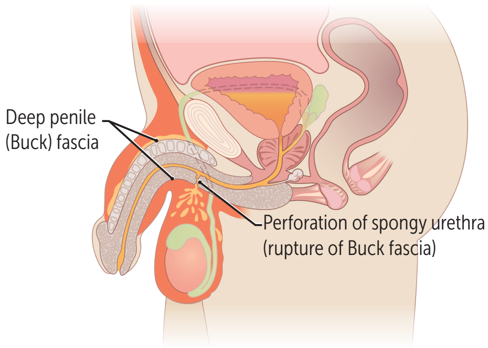
## Male reproductive anatomy



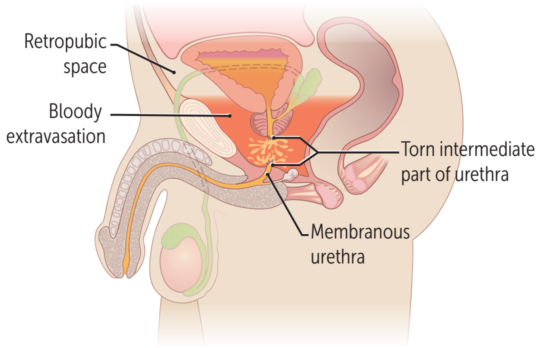




Pathway of sperm during ejaculation—
**SEVEN UP**:
**S**eminiferous tubules
**E**pididymis
**V**as deferens
**E**jaculatory ducts
(**N**othing)
**U**rethra
**P**enis

| | |
|---|---|
| **Genitourinary trauma** | Most commonly due to blunt trauma (eg, motor vehicle collision). |
| **Renal injury** | Presents with bruises, flank pain, hematuria. Caused by direct blows or lower rib fractures. |
| **Bladder injury** | Presents with hematuria, suprapubic pain, difficulty voiding.<br>▪ Superior bladder wall (dome) injury—direct trauma to full bladder (eg, seatbelt) → abrupt ↑ intravesical pressure → dome rupture (weakest part) → intraperitoneal urine accumulation. Peritoneal absorption of urine → ↑ BUN, ↑ creatinine.<br>▪ Anterior bladder wall or neck injury—pelvic fracture → perforation by bony spicules → extraperitoneal urine accumulation (retropubic space). |
| **Urethral injury** | Occurs almost exclusively in males. Presents with blood at urethral meatus, hematuria, difficulty voiding. Urethral catheterization is relatively contraindicated.<br>▪ Anterior urethral injury—perineal straddle injury → disruption of bulbar (spongy) urethra → scrotal hematoma. If Buck fascia is torn, urine escapes into perineal space.<br>▪ Posterior urethral injury—pelvic fracture → disruption at bulbomembranous junction (weakest part) → urine leakage into retropubic space and high-riding prostate. |




Anterior urethral injury

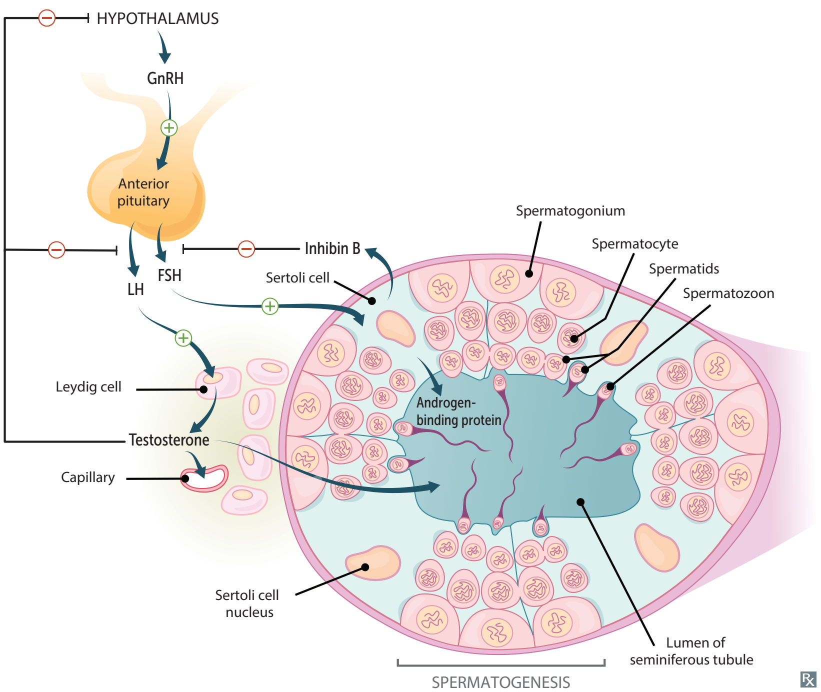


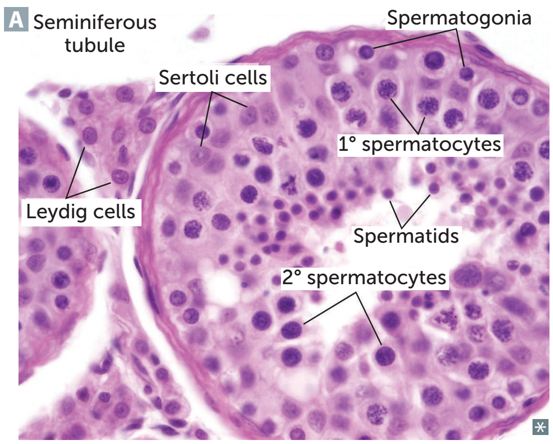

Posterior urethral injury

| | | |
|---|---|---|
| **Autonomic innervation of male sexual response** | Erection—parasympathetic nervous system (pelvic splanchnic nerves, S2-S4):<br>▪ NO → ↑ cGMP → smooth muscle relaxation → vasodilation → proerectile.<br>▪ Norepinephrine → ↑ $[Ca^{2+}]_{in}$ → smooth muscle contraction → vasoconstriction → antierectile.<br>Emission—sympathetic nervous system (hypogastric nerve, T11-L2).<br>Expulsion—visceral and somatic nerves (pudendal nerve). | Point, squeeze, and shoot.<br>S2, 3, 4 keep the penis off the floor.<br>PDE-5 inhibitors (eg, sildenafil) → ↓ cGMP breakdown. |

## Seminiferous tubules

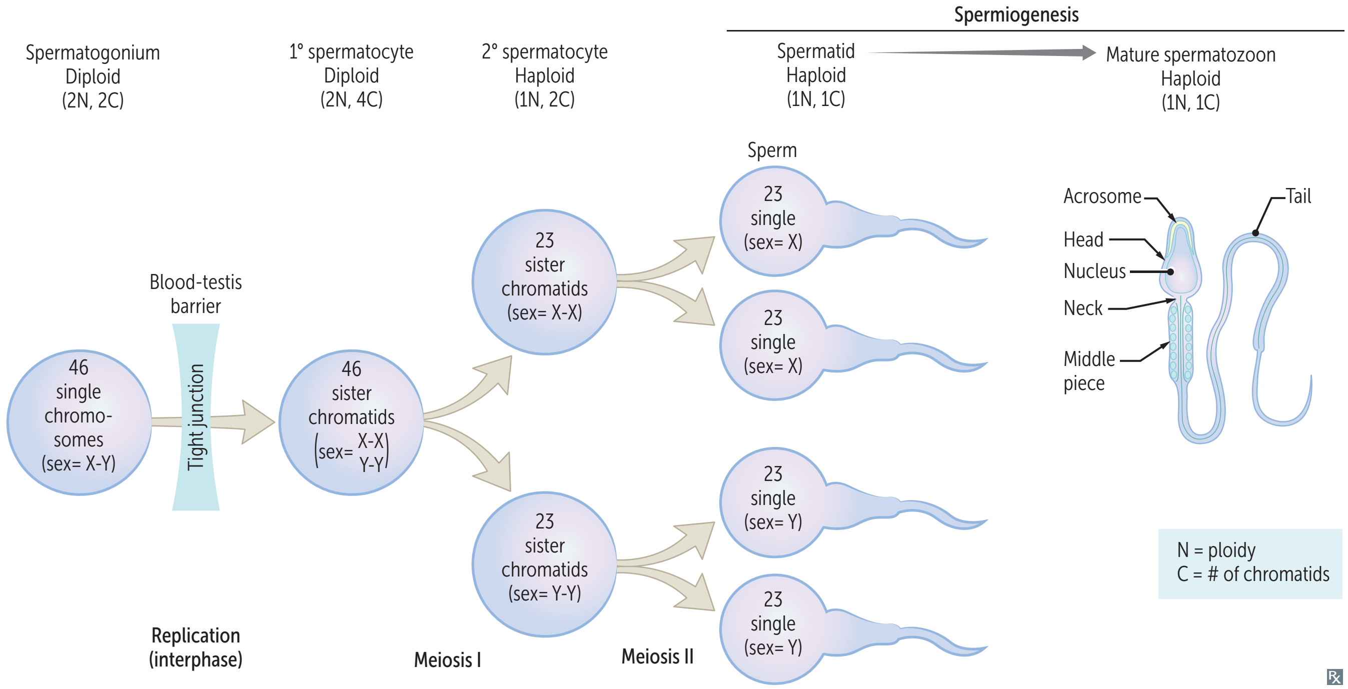
| CELL | FUNCTION | LOCATION/NOTES |
|---|---|---|
| **Spermatogonia** | Maintain germ cell pool and produce 1° spermatocytes | Line seminiferous tubules A<br>Germ cells |
| **Sertoli cells** | Secrete inhibin B → inhibit FSH<br>Secrete androgen-binding protein → maintain local levels of testosterone<br>Produce MIF<br>Tight junctions between adjacent Sertoli cells form blood-testis barrier → isolate gametes from autoimmune attack<br>Support and nourish developing spermatozoa<br>Regulate spermatogenesis<br>Temperature sensitive; ↓ sperm production and ↓ inhibin B with ↑ temperature | Line seminiferous tubules<br>Non–germ cells<br>Convert testosterone and androstenedione to estrogens via aromatase<br>Sertoli cells are temperature sensitive, line seminiferous tubules, support sperm synthesis, and inhibit FSH<br>Homolog of female granulosa cells<br>↑ temperature seen in varicocele, cryptorchidism |
| **Leydig cells** | Secrete testosterone in the presence of LH; testosterone production unaffected by temperature | Interstitium<br>Endocrine cells<br>Homolog of female theca interna cells |



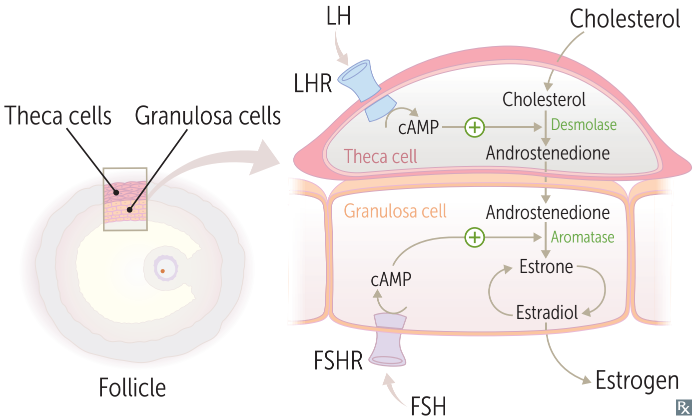
## ▶ REPRODUCTIVE—PHYSIOLOGY

| | | |
|---|---|---|
| **Spermatogenesis** | Begins at puberty with spermatogonia. Full development takes 2 months. Occurs in seminiferous tubules. Produces spermatids that undergo spermiogenesis (loss of cytoplasmic contents, gain of acrosomal cap) to form mature spermatozoa. | "Gonium" is going to be a sperm; "zoon" is "zooming" to egg.<br>Tail mobility impaired in ciliary dyskinesia/Kartagener syndrome → infertility.<br>Tail mobility normal in cystic fibrosis (in CF, absent vas deferens → infertility). |



## Estrogen

| | | |
|---|---|---|
| SOURCE | Ovary (17β-estradiol), placenta (estriol), adipose tissue (estrone via aromatization). | Potency: estradiol > estrone > estriol. |
| FUNCTION | Development of internal/external genitalia, breasts, female fat distribution.<br>Growth of follicle, endometrial proliferation, ↑ myometrial excitability.<br>Upregulation of estrogen, LH, and progesterone receptors; feedback inhibition of FSH and LH, then LH surge; stimulation of prolactin secretion, ↓ prolactin action on breasts.<br>↑ transport proteins, SHBG; ↑ HDL; ↓ LDL. | Pregnancy:<br>▪ 50-fold ↑ in estradiol and estrone<br>▪ 1000-fold ↑ in estriol (indicator of fetal well-being)<br>Estrogen receptors expressed in cytoplasm; translocate to nucleus when bound by estrogen. |

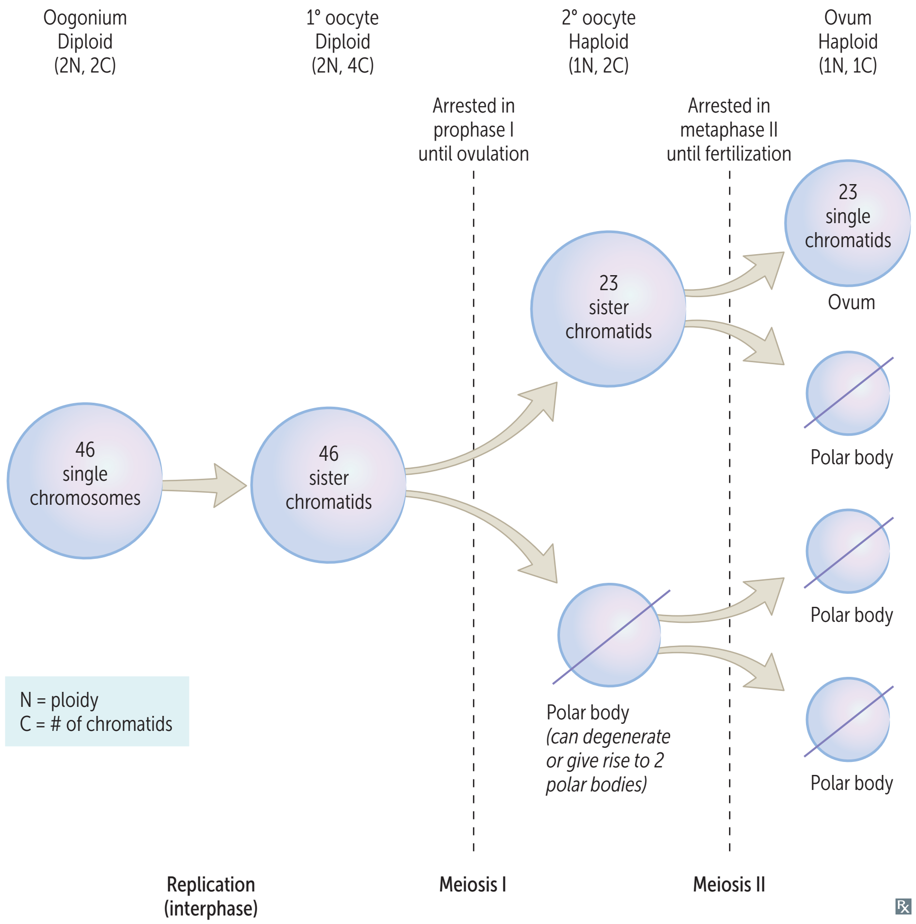



## Progesterone

| | | |
|---|---|---|
| SOURCE | Corpus luteum, placenta, adrenal cortex, testes. | Fall in estrogen and progesterone after delivery disinhibits prolactin → lactation. ↑ progesterone is indicative of ovulation.<br>**Progest**erone is **pro-gest**ation.<br>**Prolact**in is **pro-lact**ation. |
| FUNCTION | During luteal phase, prepares uterus for implantation of fertilized egg:<br>▪ Stimulation of endometrial glandular secretions and spiral artery development<br>▪ Production of thick cervical mucus → inhibits sperm entry into uterus<br>▪ Prevention of endometrial hyperplasia<br>▪ ↑ body temperature<br>▪ ↓ estrogen receptor expression<br>▪ ↓ gonadotropin (LH, FSH) secretion<br>During pregnancy:<br>▪ Maintenance of pregnancy<br>▪ ↓ myometrial excitability → ↓ contraction frequency and intensity<br>▪ ↓ prolactin action on breasts | |

## Oogenesis

1° oocytes begin meiosis I during fetal life and complete meiosis I just prior to ovulation.
Meiosis I is arrested in prophase I for years until ovulation (1° oocytes).
Meiosis II is arrested in metaphase II until fertilization (2° oocytes). "An egg met a sperm."
If fertilization does not occur within 1 day, the 2° oocyte degenerates.



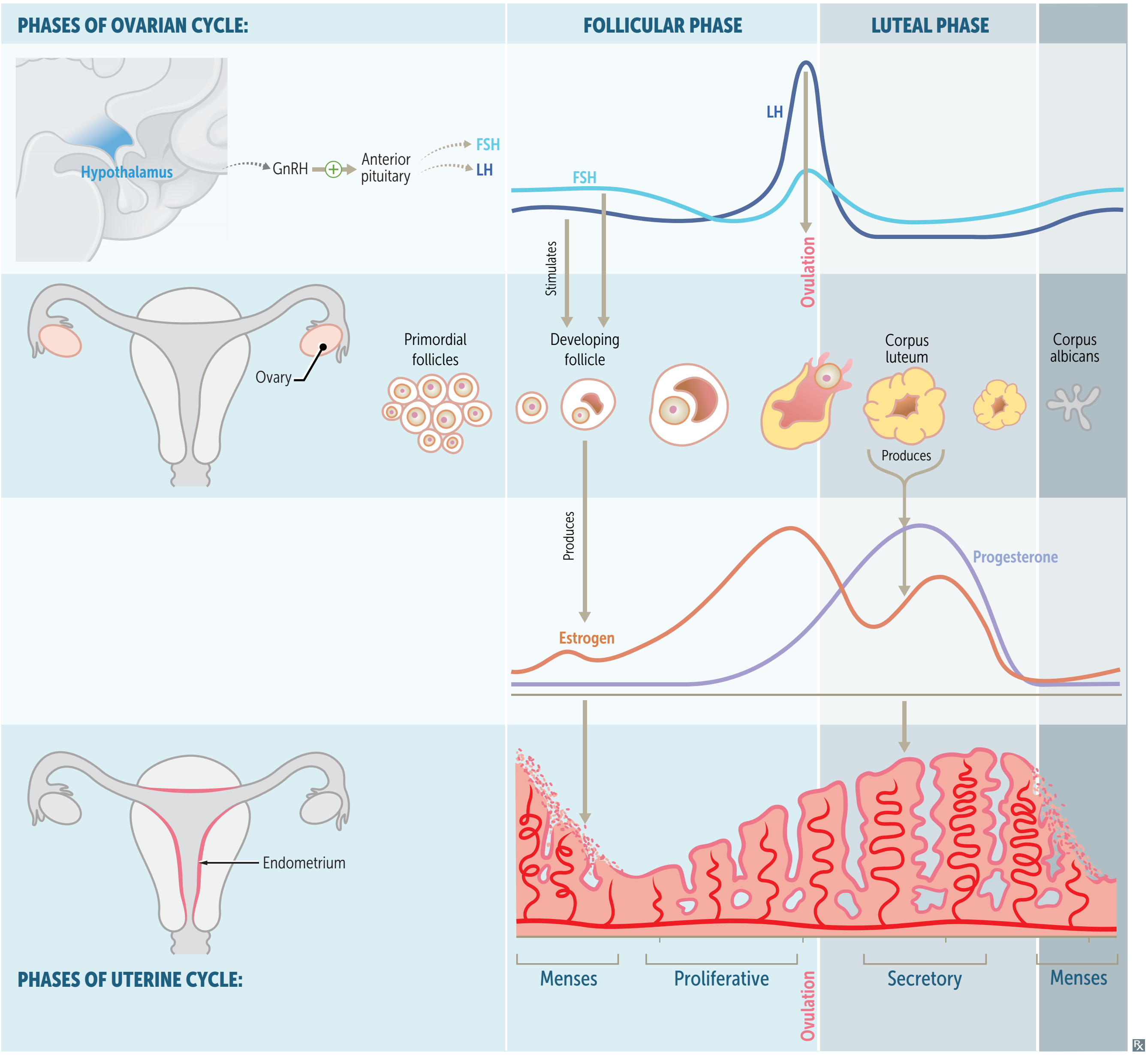

## Ovulation

↑ estrogen, ↑ GnRH receptors on anterior pituitary. Estrogen rise then stimulates LH surge → ovulation (rupture of follicle).
↑ temperature (progesterone induced).

Mittelschmerz—transient mid-cycle ovulatory pain ("middle hurts"); classically associated with peritoneal irritation (eg, follicular swelling/rupture, fallopian tube contraction). Can mimic appendicitis.

**Menstrual cycle**

**F**ollicular phase can **f**luctuate in length.
Follicular growth is fastest during 2nd week of the follicular phase.
Luteal phase is a fixed 14 days, after which menstruation occurs.
Estrogen stimulates endometrial proliferation.
Progesterone maintains endometrium to support implantation.
↓ progesterone → ↓ fertility.



**Abnormal uterine bleeding**

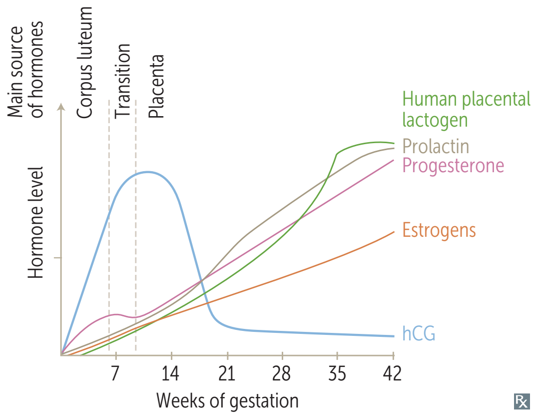
Characterized as either heavy menstrual bleeding (AUB/HMB) or intermenstrual bleeding (AUB/IMB).
These are further subcategorized by **PALM-COEIN**:
- Structural causes (**PALM**): **P**olyp, **A**denomyosis, **L**eiomyoma, or **M**alignancy/hyperplasia
- Non-structural causes (**COEIN**): **C**oagulopathy, **O**vulatory, **E**ndometrial, **I**atrogenic, **N**ot yet classified

Terms such as dysfunctional uterine bleeding, menorrhagia, oligomenorrhea are no longer recommended.

**Pregnancy**

Fertilization (conception) most commonly occurs in upper end of fallopian tube (the ampulla). Occurs within 1 day of ovulation.
Implantation in the uterine wall occurs 6 days after fertilization. Syncytiotrophoblasts secrete hCG, which is detectable in blood 1 week after fertilization and on home urine tests 2 weeks after fertilization.
Embryonic/developmental age—time since fertilization. Used in embryology.
Gestational age—time since first day of last menstrual period. Used clinically.
Gravidity ("gravida")—number of pregnancies.
Parity ("para")—number of pregnancies that resulted in live births.

Placental hormone secretion generally increases over the course of pregnancy, but hCG peaks at 8–10 weeks of gestation.




**Physiologic changes in pregnancy**

Changes that nurture the developing fetus and prepare the pregnant patient for labor and delivery. Mediated by ↑ hormones (eg, estrogen, progesterone) and mechanical effects of gravid uterus.

| | |
|---|---|
| CARDIOVASCULAR | ↓ SVR (↓ afterload) and ↑ blood volume (↑ preload) → ↑ SV → ↑ CO → ↑ placental perfusion. ↑ HR is the major contributor to ↑ CO in late pregnancy. Hemodilution → ↓ oncotic pressure → peripheral edema. |
| ENDOCRINE | Insulin resistance and hypoglycemia → ↑ lipolysis and fat utilization (to preserve glucose and amino acids for fetus). Pituitary enlargement (lactotroph hyperplasia). ↑ TBG, ↑ CBG, ↑ SHBG. |
| GASTROINTESTINAL | ↓ GI motility, ↓ LES tone, gallbladder stasis; predispose to constipation, GERD, gallstones. |
| HEMATOLOGIC | Dilutional anemia (↑↑ plasma volume, ↑ RBC mass), hypercoagulable state (to ↓ blood loss at delivery). ↑ micronutrient requirements predispose to deficiency (eg, iron, folate). |
| MUSCULOSKELETAL | Lordosis (to realign gravity center), joint laxity (to facilitate fetal descent). |
| SKIN | Hyperpigmentation (eg, melasma, linea nigra, areola darkening), striae gravidarum (stretch marks), vascular changes (eg, spider angiomas, palmar erythema, varicosities). |
| RENAL | Vasodilation → ↑ renal plasma flow → ↑ GFR → ↓ BUN and ↓ creatinine. Mild glucosuria, proteinuria. Ureter and renal pelvis dilation (hydroureter and hydronephrosis) predisposes to pyelonephritis. |
| RESPIRATORY | Respiratory center stimulation → chronic hyperventilation (to ↑ fetal $CO_2$ elimination). |

## Human chorionic gonadotropin

| | |
|---|---|
| SOURCE | Syncytiotrophoblast of placenta. |
| FUNCTION | Maintains corpus luteum (and thus progesterone) for first 8–10 weeks of gestation by acting like LH (otherwise no luteal cell stimulation → abortion). Luteal-placental shift is complete after 8–10 weeks; placenta synthesizes its own estriol and progesterone and corpus luteum degenerates.<br>Used to detect pregnancy because it appears early in urine (see above).<br>Has identical α subunit as LH, FSH, TSH (states of ↑ hCG can cause hyperthyroidism). β subunit is unique (pregnancy tests detect β subunit). hCG is ↑ in multiple gestations, hydatidiform moles, choriocarcinomas, and Down syndrome; hCG is ↓ in ectopic/failing pregnancy, Edwards syndrome, and Patau syndrome. |

## Human placental lactogen

Also called chorionic somatomammotropin.

| | |
|---|---|
| SOURCE | Syncytiotrophoblast of placenta. |
| FUNCTION | Stimulates insulin production; overall ↑ insulin resistance. Gestational diabetes can occur if pancreatic function cannot overcome the insulin resistance. |

## Apgar score

| | Score 2 | Score 1 | Score 0 |
|---|---|---|---|
| **A**ppearance | Pink | Extremities blue | Pale or blue |
| **P**ulse | ≥ 100 bpm | < 100 bpm | No pulse |
| **G**rimace | Cries and pulls away | Grimaces or weak cry | No response to stimulation |
| **A**ctivity | Active movement | Arms, legs flexed | No movement |
| **R**espiration | Strong cry | Slow, irregular | No breathing |

Assessment of newborn vital signs following delivery via a 10-point scale evaluated at 1 minute and 5 minutes. **Apgar** score is based on **a**ppearance, **p**ulse, **g**rimace, **a**ctivity, and **r**espiration. Apgar scores < 7 may require further evaluation. If Apgar score remains low at later time points, there is ↑ risk the child will develop long-term neurologic damage.

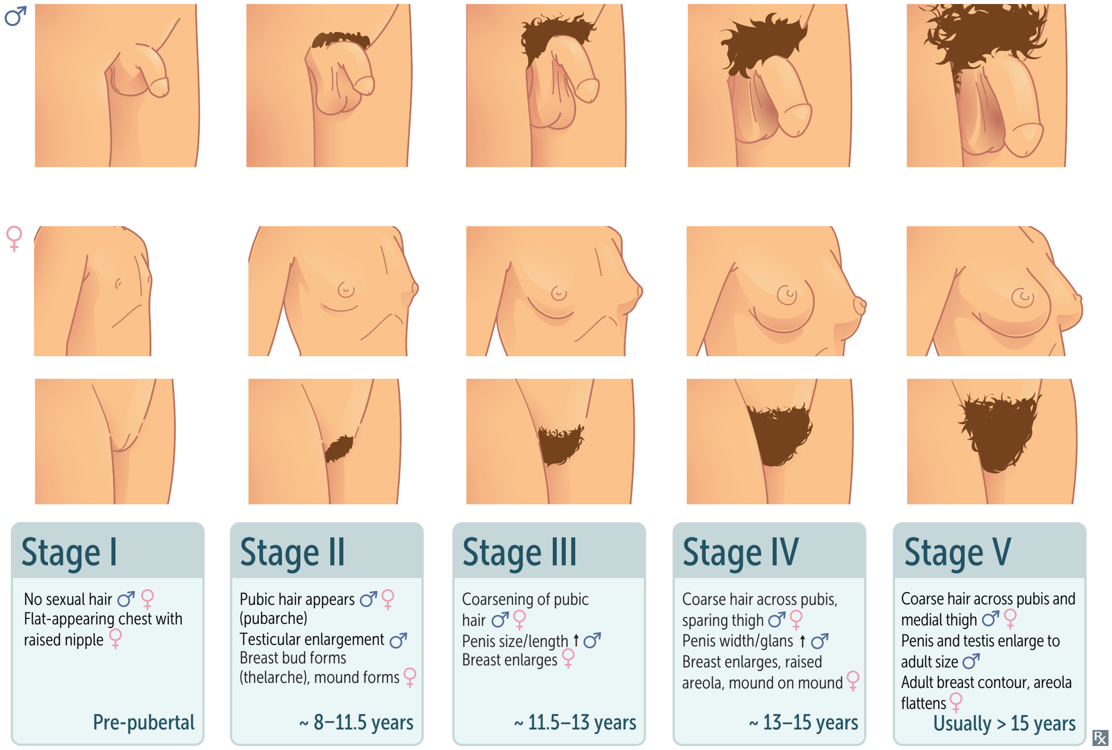
## Low birth weight

Defined as < 2500 g. Caused by prematurity or intrauterine growth restriction (IUGR). Associated with ↑ risk of sudden infant death syndrome (SIDS) and with ↑ overall mortality.

| | | |
|---|---|---|
| **Lactation** | After parturition and delivery of placenta, rapid ↓ in estrogen and progesterone disinhibits prolactin → initiation of lactation. Suckling is required to maintain milk production and ejection, since ↑ nerve stimulation → ↑ oxytocin and prolactin.<br>Prolactin—induces and maintains lactation and ↓ reproductive function.<br>Oxytocin—assists in milk letdown; also promotes uterine contractions.<br>Breast milk is the ideal nutrition for infants < 6 months old. Contains immunoglobulins (conferring passive immunity; mostly IgA), macrophages, lymphocytes. Breast milk reduces infant infections and is associated with ↓ risk for child to develop asthma, allergies, diabetes mellitus, and obesity. Guidelines recommend exclusively breastfed infants get vitamin D and possibly iron supplementation.<br>Breastfeeding facilitates bonding with the child. Breastfeeding or donating milk ↓ risk of breast and ovarian cancers. | |
| **Menopause** | Diagnosed by amenorrhea for 12 months.<br>↓ estrogen production due to age-linked decline in number of ovarian follicles. Average age at onset is 51 years (earlier in people who smoke tobacco).<br>Usually preceded by 4–5 years of abnormal menstrual cycles. Source of estrogen (estrone) after menopause becomes peripheral conversion of androgens, ↑ androgens → hirsutism.<br>↑↑ FSH is specific for menopause (loss of negative feedback on FSH due to ↓ estrogen). | Hormonal changes: ↓ estrogen, ↑↑ FSH, ↑ LH (no surge), ↑ GnRH.<br>Causes **HAVOCS**: **H**ot flashes (most common), **A**trophy of the **V**agina, **O**steoporosis, **C**oronary artery disease, **S**leep disturbances.<br>Menopause before age 40 suggests 1° ovarian insufficiency (premature ovarian failure); may occur in females who have received chemotherapy and/or radiation therapy. |
| **Androgens** | Testosterone, dihydrotestosterone (DHT), androstenedione. | |
| SOURCE | DHT and testosterone (testis), **and**rostenedione (**ad**renal) | Potency: DHT > testosterone > androstenedione. |
| FUNCTION | Testosterone:<br>▪ Differentiation of epididymis, vas deferens, seminal vesicles (internal genitalia, except prostate)<br>▪ Growth spurt: penis, seminal vesicles, sperm, muscle, RBCs<br>▪ Deepening of voice<br>▪ Closing of epiphyseal plates (via estrogen converted from testosterone)<br>▪ Libido<br>DHT:<br>▪ Early—differentiation of penis, scrotum, prostate<br>▪ Late—prostate growth, balding, sebaceous gland activity | Testosterone is converted to DHT by 5α-reductase, which is inhibited by finasteride.<br>In the male, **a**ndrogens are converted to **e**strogens by **a**romatas**e** (primarily in adipose tissue and testes).<br>Anabolic-androgenic steroid use—↑ fat-free mass, muscle strength, performance. Suspect in males who present with changes in behavior (eg, aggression), acne, gynecomastia, ↑ Hb and Hct, small testes (exogenous testosterone → hypothalamic-pituitary-gonadal axis inhibition → ↓ intratesticular testosterone → ↓ testicular size, ↓ sperm count, azoospermia). Females may present with virilization (eg, hirsutism, acne, breast atrophy, male pattern baldness). |

## Tanner stages of sexual development

Tanner stage is assigned independently to genitalia, pubic hair, and breast (eg, a person can have Tanner stage 2 genitalia, Tanner stage 3 pubic hair). Earliest detectable secondary sexual characteristic is breast bud development in females, testicular enlargement in males.




## Precocious puberty

Appearance of 2° sexual characteristics (eg, adrenarche, thelarche, menarche) before age 8 years in females and 9 years in males. ↑ sex hormone exposure or production → ↑ linear growth, somatic and skeletal maturation (eg, premature closure of epiphyseal plates → short stature). Types include:

- Central precocious puberty (↑ GnRH secretion): idiopathic (most common; early activation of hypothalamic-pituitary gonadal axis), CNS tumors.
- Peripheral precocious puberty (GnRH-independent; ↑ sex hormone production or exposure to exogenous sex steroids): congenital adrenal hyperplasia, estrogen-secreting ovarian tumor (eg, granulosa cell tumor), Leydig cell tumor, McCune-Albright syndrome.

## ▸ REPRODUCTIVE—PATHOLOGY

| | | |
|---|---|---|
| **Sex chromosome disorders** | Aneuploidy most commonly due to meiotic nondisjunction. | |
| **Klinefelter syndrome**<br>A  | Male, 47,XXY.<br>Testicular atrophy (small, firm testes), tall stature with eunuchoid proportions (delayed epiphyseal closure → ↑ long bone length), gynecomastia, female hair distribution A.<br>May present with developmental delay.<br>Presence of inactivated X chromosome (Barr body). Common cause of hypogonadism seen in infertility workup. ↑ risk of breast cancer. | Dysgenesis of seminiferous tubules → ↓ inhibin B → ↑ FSH.<br>Abnormal Leydig cell function → ↓ testosterone → ↑ LH → ↑ estrogen. |
| **Turner syndrome**<br>B  | Female, 45,XO.<br>**Sh**ort stature (associated with ***SH***OX gene, preventable with growth hormone therapy), ovarian dysgenesis (streak ovary), shield chest B, bicuspid aortic valve, coarctation of the aorta (femoral < brachial pulse), lymphatic defects (result in webbed neck or cystic hygroma; lymphedema in feet, hands), horseshoe kidney, high-arched palate, shortened 4th metacarpals.<br>Most common cause of 1° amenorrhea. No Barr body. | Menopause before menarche.<br>↓ estrogen leads to ↑ LH, FSH.<br>Sex chromosome (X, or rarely Y) loss often due to nondisjunction during meiosis or mitosis.<br>Meiosis errors usually occur in paternal gametes → sperm missing the sex chromosome.<br>Mitosis errors occur after zygote formation → loss of sex chromosome in some but not all cells → mosaic karyotype (eg. 45,X/46XX).<br>(45,X/46,XY) mosaicism associated with increased risk for gonadoblastoma.<br>Pregnancy is possible in some cases (IVF, exogenous estradiol-17β and progesterone). |
| **Double Y males** | 47, XYY.<br>Phenotypically normal (usually undiagnosed), very tall. Normal fertility. May be associated with severe acne, learning disability, autism spectrum disorders. | |
| **Ovotesticular disorder of sex development** | 46,XX > 46,XY.<br>Both ovarian and testicular tissue present (ovotestis); ambiguous genitalia. Previously called true hermaphroditism. | |

**Diagnosing disorders of sex hormones**

| Testosterone | LH | Diagnosis |
|---|---|---|
| ↑ | ↑ | Defective androgen receptor |
| ↑ | ↓ | Testosterone-secreting tumor, exogenous steroids |
| ↓ | ↑ | Hypergonadotropic hypogonadism (1°) |
| ↓ | ↓ | Hypogonadotropic hypogonadism (2°) |

**Other disorders of sex development**

Disagreement between the phenotypic sex (external genitalia, influenced by hormonal levels) and the gonadal sex (testes vs ovaries, corresponds with Y chromosome). Formerly called hermaphroditism and pseudohermaphroditism; now most commonly referred to as intersex.

**46,XX DSD**

Ovaries present, but external genitalia are virilized or ambiguous. Due to excessive and inappropriate exposure to androgenic steroids during early gestation (eg, congenital adrenal hyperplasia or exogenous administration of androgens during pregnancy).

**46,XY DSD**

Testes present, but external genitalia are female or ambiguous. Most common form is androgen insensitivity syndrome (testicular feminization).

**Disorders by physical characteristics**

| UTERUS | BREASTS | DISORDERS |
|---|---|---|
| ⊕ | ⊖ | Hypergonadotropic hypogonadism (eg, Turner syndrome, genetic mosaicism, pure gonadal dysgenesis)<br>Hypogonadotropic hypogonadism (eg, CNS lesions, Kallmann syndrome) |
| ⊖ | ⊕ | Uterovaginal agenesis in genotypic female or androgen insensitivity in genotypic male |
| ⊖ | ⊖ | Male genotype with insufficient production of testosterone |

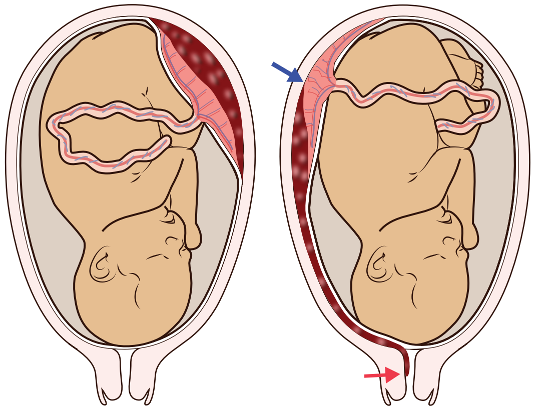
| | |
|---|---|
| **Placental aromatase deficiency** | Inability to synthesize estrogens from androgens. Masculinization of female (46,XX DSD) infants (ambiguous genitalia), ↑ serum testosterone and androstenedione. Can present with virilization of pregnant patient (fetal androgens cross the placenta). |
| **Androgen insensitivity syndrome** | Defect in androgen receptor resulting in female-appearing genetic male (46,XY DSD); female external genitalia with scant axillary and pubic hair, rudimentary vagina; uterus and fallopian tubes absent due to persistence of anti-Müllerian hormone from testes. Patients develop normal functioning testes (often found in labia majora; surgically removed to prevent malignancy). ↑ testosterone, estrogen, LH (vs sex chromosome disorders). |
| **5α-reductase deficiency** | Autosomal recessive; sex limited to genetic males (46,XY DSD). Inability to convert testosterone to DHT. Ambiguous genitalia until puberty, when ↑ testosterone causes masculinization/↑ growth of external genitalia. Testosterone/estrogen levels are normal; LH is normal or ↑. Internal genitalia are normal. |
| **Kallmann syndrome** | Failure to complete puberty; a form of hypogonadotropic hypogonadism. Defective migration of neurons and subsequent failure of olfactory bulbs to develop → ↓ synthesis of GnRH in the hypothalamus; hyposmia/anosmia; ↓ GnRH, FSH, LH, testosterone. Infertility (low sperm count in males; amenorrhea in females). |

## Pregnancy complications

**Abruptio placentae**

Premature separation (partial or complete) of placenta from uterine wall before delivery of infant. Risk factors: trauma (eg, motor vehicle accident), smoking, hypertension, preeclampsia, cocaine use.

Presentation: **abrupt**, painful bleeding (concealed or apparent) in third trimester; possible DIC (mediated by tissue factor activation), shock, fetal distress. May be life threatening for patient and fetus.



Complete abruption with concealed hemorrhage

Partial abruption (blue arrow) with apparent hemorrhage (red arrow)

**Placenta accreta spectrum**

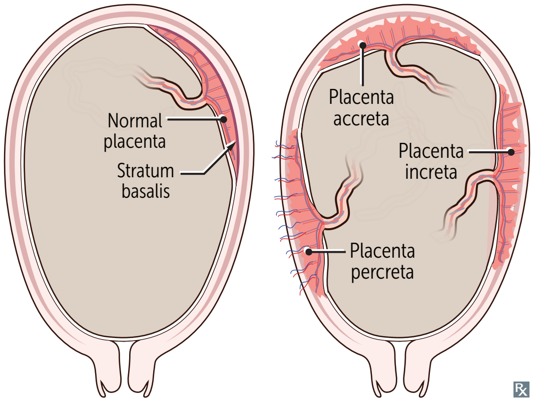
Defective decidual layer → abnormal attachment and separation after delivery. Risk factors: prior C-section or uterine surgery involving myometrium, inflammation, placenta previa, advanced age during pregnancy, multiparity. Three types distinguishable by the depth of penetration:

Placenta **accreta**—placenta **attaches** to myometrium without penetrating it; most common type.

Placenta **increta**—placenta penetrates **into** myometrium.

Placenta **percreta**—placenta penetrates ("**perforates**") through myometrium and into uterine serosa (invades entire uterine wall); can result in placental attachment to rectum or bladder (can result in hematuria).

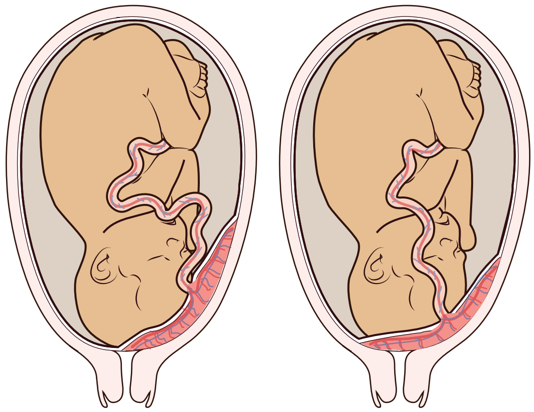
Presentation: often detected on ultrasound prior to delivery. No separation of placenta after delivery → postpartum hemorrhage (can cause Sheehan syndrome).




**Placenta previa**

Attachment of placenta over internal cervical os. Risk factors: multiparity, prior C-section. Associated with painless third-trimester bleeding. A "**previ**ew" of the **placenta** is visible through cervix.

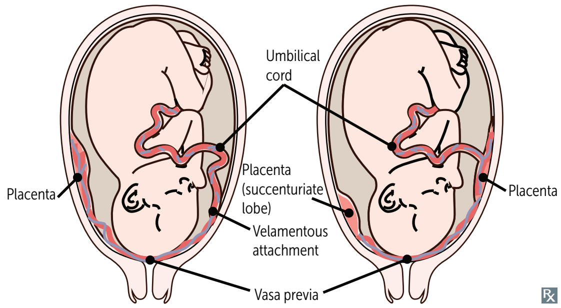
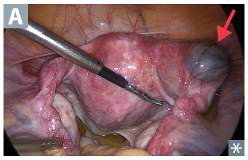
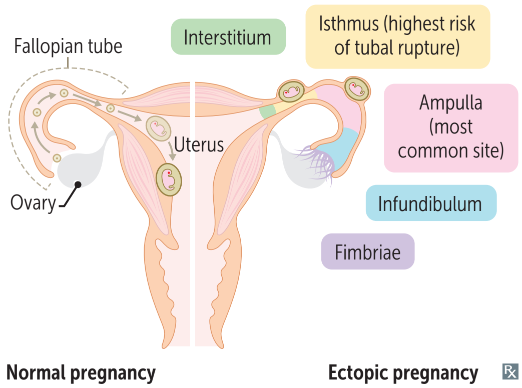
Low-lying placenta is located < 2 cm from, but not covering, the internal cervical os.



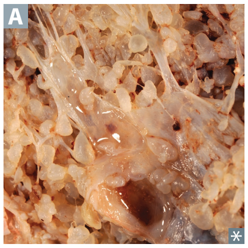
Partial placenta previa

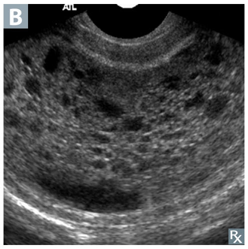
Complete placenta previa

## Pregnancy complications *(continued)*

| | | |
|---|---|---|
| **Vasa previa** | Fetal vessels run over, or in close proximity to, cervical os. May result in vessel rupture, exsanguination, fetal death. Presents with triad of membrane rupture, painless vaginal bleeding, fetal bradycardia (< 110 beats/min). Emergency C-section usually indicated. Frequently associated with velamentous umbilical cord insertion (cord inserts in chorioamniotic membrane rather than placenta → fetal vessels travel to placenta unprotected by Wharton jelly). |   |
| **Postpartum hemorrhage** | Due to 4 T's: **t**one (uterine atony → soft, boggy uterus; most common), **t**rauma (lacerations, incisions, uterine rupture), **t**hrombin (coagulopathy), **t**issue (retained products of conception).<br>Treatment: uterine massage, oxytocin. If refractory, surgical ligation of uterine or internal iliac artery (will preserve fertility since ovarian arteries provide collateral circulation). | |
| **Ectopic pregnancy**<br> | Implantation of fertilized ovum in a site other than the uterus, most often in ampulla of fallopian tube A. Risk factors: tubal pathologies (eg, scarring from salpingitis [PID] or surgery), previous ectopic pregnancy, IUD, IVF.<br>Presents with first-trimester bleeding and/or lower abdominal pain. Often clinically mistaken for appendicitis. Suspect in patients with history of amenorrhea, lower-than-expected rise in hCG based on dates. Confirm with ultrasound, which may show extraovarian adnexal mass.<br>Treatment: methotrexate, surgery. |   |

## Hydatidiform mole

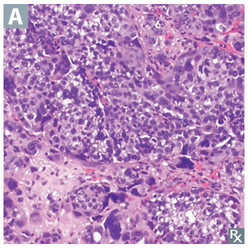




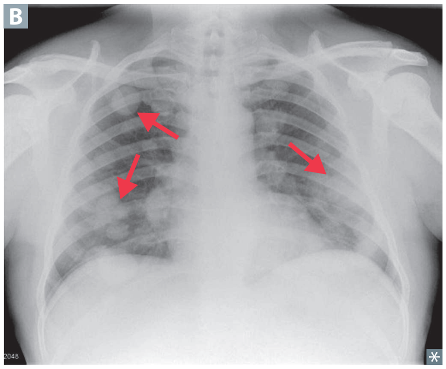
Cystic swelling of chorionic villi and proliferation of chorionic epithelium (only trophoblast).
Presents with vaginal bleeding, emesis, uterine enlargement more than expected, pelvic pressure/pain. Associated with hCG-mediated sequelae: early preeclampsia (before 20 weeks of gestation), theca-lutein cysts, hyperemesis gravidarum, hyperthyroidism.
Treatment: dilation and curettage +/– methotrexate. Monitor hCG.

| | Complete mole | Partial mole |
|---|---|---|
| KARYOTYPE | 46,XX (most common); 46,XY | 69,XXX; 69,XXY; 69,XYY |
| COMPONENTS | Most commonly enucleated egg + single sperm (subsequently duplicates paternal DNA) | 2 sperm + 1 egg |
| HISTOLOGY | Hydropic villi, circumferential and diffuse trophoblastic proliferation | Only some villi are hydropic, focal/minimal trophoblastic proliferation |
| FETAL PARTS | No | Yes (**part**ial = fetal **parts**) |
| STAINING FOR P57 PROTEIN | $\ominus$ (paternally imprinted) | $\oplus$ (maternally expressed)<br>**P**artial mole is **P**57 **p**ositive |
| UTERINE SIZE | $\uparrow$ | — |
| hCG | $\uparrow\uparrow\uparrow\uparrow$ | $\uparrow$ |
| IMAGING | "Honeycombed" uterus or "clusters of grapes" A, "snowstorm" B on ultrasound | Fetal parts |
| RISK OF INVASIVE MOLE | 15–20% | < 5% |
| RISK OF CHORIOCARCINOMA | 2% | Rare |

## Choriocarcinoma



Rare; can develop during or after pregnancy in parent or baby. Malignancy of trophoblastic tissue A (cytotrophoblasts, syncytiotrophoblasts); **no** chorionic villi present. $\uparrow$ frequency of bilateral/multiple theca-lutein cysts. Presents with abnormal $\uparrow$ hCG, shortness of breath, hemoptysis. Hematogenous spread to lungs → "cannonball" metastases B.
Treatment: methotrexate.



## Hypertension in pregnancy

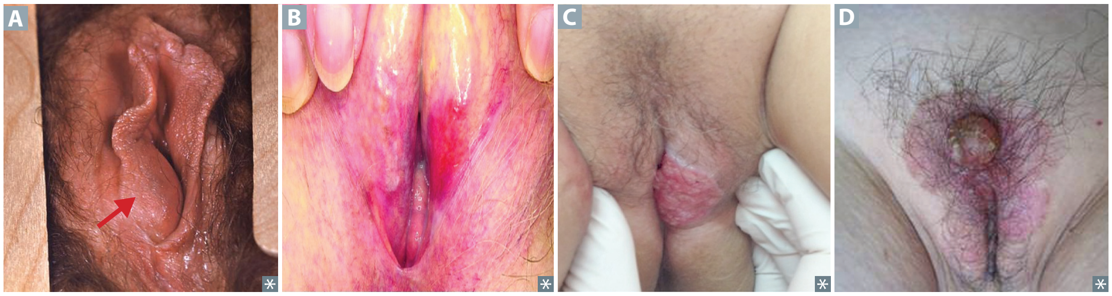
| | |
|---|---|
| **Gestational hypertension** | BP > 140/90 mm Hg after 20 weeks of gestation. No preexisting hypertension. No proteinuria or end-organ damage. Hypertension prior to 20 weeks of gestation suggests chronic hypertension.<br>Treatment: antihypertensives (**H**ydralazine, α-**m**ethyldopa, **l**abetalol, **n**ifedipine), deliver at 37–39 weeks. **H**ypertensive **m**oms **l**ove **n**ifedipine. |
| **Preeclampsia** | New-onset hypertension with either proteinuria or end-organ dysfunction after 20 weeks' gestation (onset of preeclampsia < 20 weeks of gestation may suggest molar pregnancy).<br>Caused by abnormal placental spiral arteries → endothelial dysfunction, vasoconstriction, ischemia. ↑ incidence in patients with history of preeclampsia, chronic hypertension, diabetes, chronic kidney disease, autoimmune disorders (eg, antiphospholipid syndrome), age > 35 years.<br>Complications: placental abruption, coagulopathy, renal failure, pulmonary edema, uteroplacental insufficiency; may lead to eclampsia and/or HELLP syndrome.<br>Treatment: antihypertensives, IV magnesium sulfate (to prevent seizure); definitive is delivery. |
| **Eclampsia** | Preeclampsia with seizures. Death due to stroke, intracranial hemorrhage, ARDS.<br>Treatment: IV magnesium sulfate, antihypertensives, immediate delivery. |
| **HELLP syndrome** | Preeclampsia with thrombotic microangiopathy of the liver. **H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets. May occur in the absence of hypertension and proteinuria. Blood smear shows schistocytes. Can lead to hepatic subcapsular hematomas (rupture → severe hypotension) and DIC (due to release of tissue factor from injured placenta).<br>Treatment: immediate delivery. |

| | |
|---|---|
| **Supine hypotensive syndrome** | Also called aortocaval compression syndrome. Seen at > 20 weeks of gestation. Supine position → compression of patient's abdominal aorta and IVC by gravid uterus → ↓ placental perfusion (can lead to pregnancy loss) and ↓ venous return (hypotension). |

| | | |
|---|---|---|
| **Gynecologic tumor epidemiology** | Incidence (US)—endometrial > ovarian > cervical; cervical cancer is more common worldwide due to lack of screening or HPV vaccination.<br>Prognosis: **C**ervical (**best** prognosis, diagnosed < 45 years old) > **E**ndometrial (middle-aged, about 55 years old) > **O**varian (**worst** prognosis, > 65 years). | **CEO**s often go from **best** to **worst** as they get older. |

## Vulvar pathology

| | |
|---|---|
| **Non-neoplastic** | |
| **Bartholin cyst and abscess** | Due to blockage of Bartholin gland duct causing accumulation of gland fluid. May lead to abscess 2° to obstruction and inflammation A. Usually in reproductive-age females. |
| **Lichen sclerosus** | Thinning of epidermis with fibrosis/sclerosis of dermis. Presents with porcelain-white plaques with a red or violet border. Skin fragility with erosions can be observed B. Most common in postmenopausal females. Benign, but slightly increased risk for SCC. |
| **Lichen simplex chronicus** | Hyperplasia of vulvar squamous epithelium. Presents with leathery, thick vulvar skin with enhanced skin markings due to chronic rubbing or scratching. Benign, no risk of SCC. |
| **Neoplastic** | |
| **Vulvar carcinoma** | Carcinoma from squamous epithelial lining of vulva C. Rare. Presents with leukoplakia, biopsy often required to distinguish carcinoma from other causes.<br>HPV-related vulvar carcinoma—associated with high-risk HPV types 16, 18. Risk factors: multiple partners, early coitarche. Usually in reproductive-age females.<br>Non-HPV vulvar carcinoma—usually from long-standing lichen sclerosus. Females > 70 years old. |
| **Extramammary Paget disease** | Intraepithelial adenocarcinoma. Carcinoma in situ, low risk of underlying carcinoma (vs Paget disease of the breast, which is always associated with underlying carcinoma). Presents with pruritus, erythema, crusting, ulcers D. |



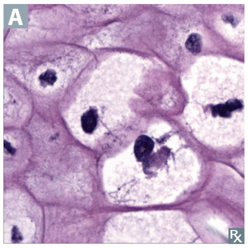

| | |
|---|---|
| **Imperforate hymen** | Incomplete degeneration of the central portion of the hymen. Accumulation of vaginal mucus at birth → self-resolving bulge in introitus. If untreated, leads to 1° amenorrhea, cyclic abdominal pain, hematocolpos (accumulation of menstrual blood in vagina → bulging and bluish hymenal membrane). |

## Vaginal tumors

| | |
|---|---|
| **Squamous cell carcinoma** | Usually 2° to cervical SCC; 1° vaginal carcinoma rare. |
| **Clear cell adenocarcinoma** | Arises from vaginal adenosis (persistence of glandular columnar epithelium in upper 2/3 of vagina), found in females who had exposure to diethylstilbestrol in utero. |
| **Sarcoma botryoides** | Embryonal rhabdomyosarcoma variant. Affects females < 4 years old; spindle-shaped cells; desmin ⊕. Presents with clear, grape-like, polypoid mass emerging from vagina. |

## Cervical pathology

### Dysplasia and carcinoma in situ




Disordered epithelial growth; begins at basal layer of squamocolumnar junction (transformation zone) and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (severe, irreversible dysplasia or carcinoma in situ), depending on extent of dysplasia. Associated with HPV-16 and HPV-18, which produce both the E6 gene product (inhibits *TP53*) and E7 gene product (inhibits *pRb*) (6 before 7; P before R). Koilocytes (cells with wrinkled "raisinoid" nucleus and perinuclear halo A) are pathognomonic of HPV infection. May progress slowly to invasive carcinoma if left untreated. Typically asymptomatic (detected with Pap smear) or presents as abnormal vaginal bleeding (often postcoital).

Risk factors: multiple sexual partners, HPV, smoking, early coitarche, DES exposure, immunocompromise (eg, HIV, transplant).

### Invasive carcinoma

Often squamous cell carcinoma. Pap smear can detect cervical dysplasia before it progresses to invasive carcinoma. Diagnose via colposcopy and biopsy. Lateral invasion can block ureters → hydronephrosis → renal failure.

## Primary ovarian insufficiency

Also called premature ovarian failure.

Premature atresia of ovarian follicles in females of reproductive age. Most often idiopathic; associated with chromosomal abnormalities (especially in females < 30 years), autoimmunity. Need karyotype screening. Patients present with signs of menopause after puberty but before age 40. ↓ estrogen, ↑ LH, ↑ FSH.

## Most common causes of anovulation

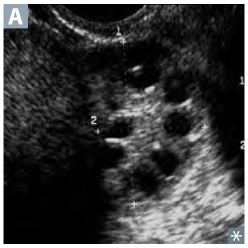
Pregnancy, polycystic ovarian syndrome, obesity, HPO axis abnormalities/immaturity, premature ovarian failure, hyperprolactinemia, thyroid disorders, eating disorders, competitive athletics, Cushing syndrome, adrenal insufficiency, chromosomal abnormalities (eg, Turner syndrome).

## Functional hypothalamic amenorrhea

Also called exercise-induced amenorrhea. Severe caloric restriction, ↑ energy expenditure, and/or stress → functional disruption of pulsatile GnRH secretion → ↓ LH, FSH, estrogen. Pathogenesis includes ↓ leptin (due to ↓ fat) and ↑ cortisol (stress, excessive exercise).

Associated with eating disorders and "female athlete triad" (↓ calorie availability/excessive exercise, ↓ bone mineral density, menstrual dysfunction).

## Polycystic ovarian syndrome




Hyperinsulinemia and/or insulin resistance hypothesized to alter hypothalamic hormonal feedback response → ↑ LH:FSH, ↑ androgens (eg, testosterone) from theca interna cells, ↓ rate of follicular maturation → unruptured follicles (cysts) + anovulation. Common cause of ↓ fertility in females.

Enlarged, bilateral cystic ovaries A; presents with amenorrhea/oligomenorrhea, hirsutism, acne, ↓ fertility. Associated with obesity, acanthosis nigricans. ↑ risk of endometrial cancer 2° to unopposed estrogen from repeated anovulatory cycles.

Treatment: cycle regulation via weight reduction (↓ peripheral estrone formation), OCPs (prevent endometrial hyperplasia due to unopposed estrogen); clomiphene (ovulation induction); spironolactone, finasteride, flutamide to treat hirsutism.

**Primary dysmenorrhea** Painful menses, caused by uterine contractions to ↓ blood loss → ischemic pain. Mediated by prostaglandins. Treatment: NSAIDs.

## Ovarian cysts

| | |
|---|---|
| **Follicular cyst** | Distention of unruptured Graafian follicle. May be associated with hyperestrogenism, endometrial hyperplasia. Most common ovarian mass in young females. |
| **Theca lutein cyst** | Also called hyperreactio luteinalis. Often bilateral/multiple. Due to hCG overstimulation. Associated with choriocarcinoma and hydatidiform moles. |

## Ovarian tumors

Most common adnexal mass in females > 55 years old. Present with abdominal distention, bowel obstruction, pleural effusion.

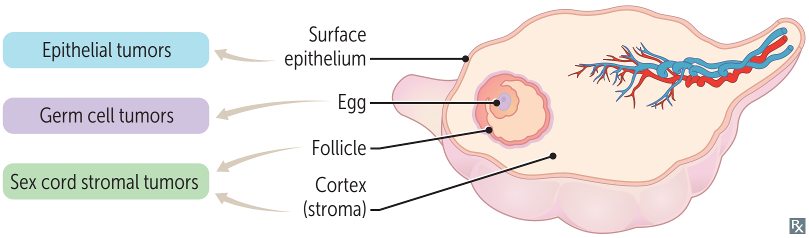
Risk ↑ with advanced age, infertility, endometriosis, PCOS, genetic predisposition (eg, *BRCA1* or *BRCA2* mutations, Lynch syndrome, strong family history).

Risk ↓ with previous pregnancy, history of breastfeeding, OCPs, tubal ligation.

Epithelial tumors are typically serous (lined by serous epithelium natively found in fallopian tubes, and often bilateral) or mucinous (lined by mucinous epithelium natively found in cervix). Monitor response to therapy/relapse by measuring CA 125 levels (not good for screening).

Germ cell tumors can differentiate into somatic structures (eg, teratomas), or extra-embryonic structures (eg, yolk sac tumors), or can remain undifferentiated (eg, dysgerminoma).

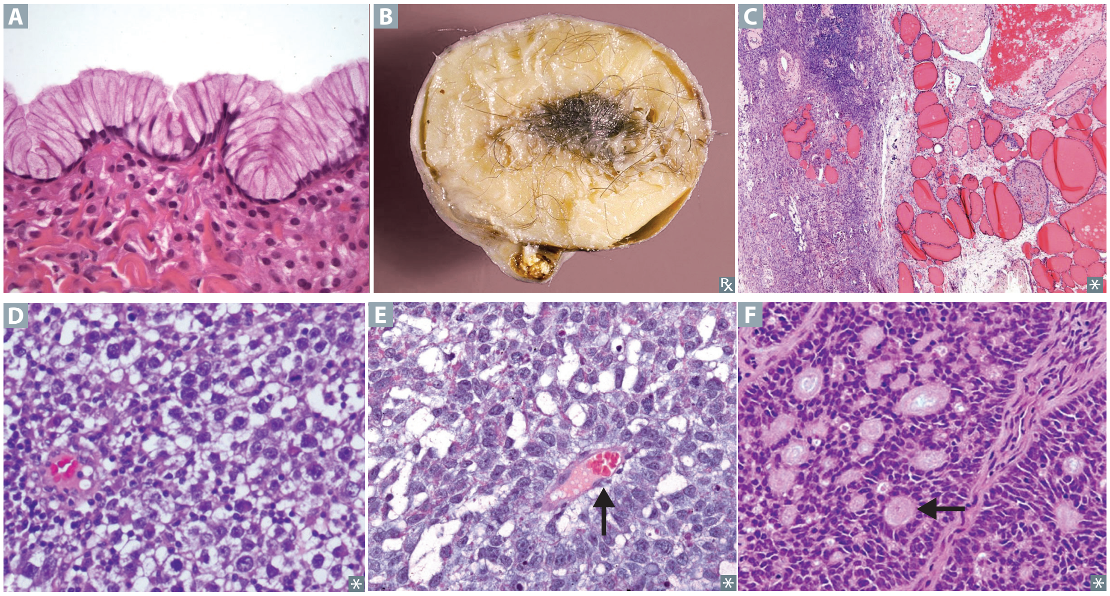
Sex cord stromal tumors develop from embryonic sex cord (develops into theca and granulosa cells of follicle, Sertoli and Leydig cells of seminiferous tubules) and stromal (ovarian cortex) derivatives.




| TYPE | CHARACTERISTICS |
|---|---|
| **Epithelial tumors** | |
| **Serous cystadenoma** | Benign. Most common ovarian neoplasm. |
| **Mucinous cystadenoma** | Benign. Multiloculated, large. Lined by mucus-secreting epithelium A. Can result in pseudomyxoma peritonei intraperitoneal accumulation of mucinous material. |
| **Brenner tumor** | Usually benign. Solid, pale yellow-tan tumor that appears encapsulated. “Coffee bean” nuclei on H&E stain. |
| **Serous carcinoma** | Most common malignant ovarian neoplasm. Psammoma bodies. |
| **Mucinous carcinoma** | Malignant. Rare. May be metastatic from appendiceal or other GI tumors. |

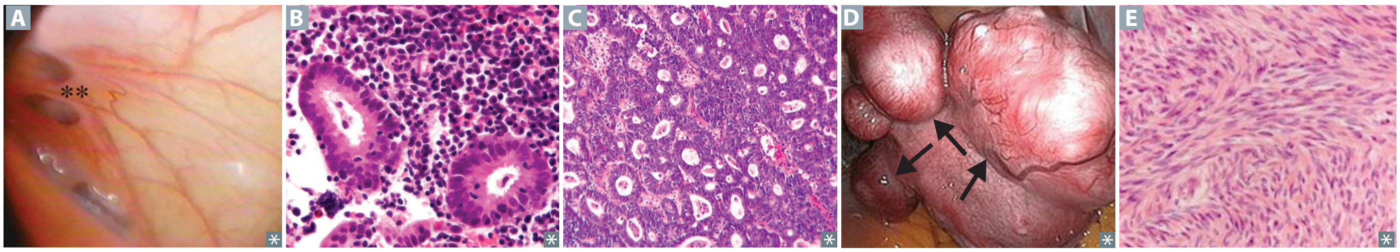
### Ovarian tumors *(continued)*

| TYPE | CHARACTERISTICS |
|---|---|
| **Germ cell tumors** | |
| **Mature cystic teratoma** | Also called dermoid cyst. Benign. Most common ovarian tumor in young females. Cystic mass with elements from all 3 germ layers (eg, teeth, hair, sebum) B. May be painful 2° to ovarian enlargement or torsion. Monodermal form with thyroid tissue (struma ovarii C) may present with hyperthyroidism. Malignant transformation rare (usually to squamous cell carcinoma). |
| **Immature teratoma** | Malignant, aggressive. Contains fetal tissue, neuroectoderm. Commonly diagnosed before age 20. Typically represented by immature/embryonic-like neural tissue. |
| **Dysgerminoma** | Malignant. Most common in adolescents. Equivalent to male seminoma but rarer. Sheets of uniform "fried egg" cells D. Tumor markers: ↑ hCG, ↑ LDH. |
| **Yolk sac tumor** | Also called endodermal sinus tumor. Malignant, aggressive. Yellow, friable (hemorrhagic) mass. 50% have Schiller-Duval bodies (resemble glomeruli, arrow in E). Tumor marker: ↑ AFP. Occurs in children and young adult females. |
| **Sex cord stromal tumors** | |
| **Fibroma** | Benign. Bundle of spindle-shaped fibroblasts.<br>Meigs syndrome—triad of ovarian fibroma, ascites, pleural effusion. "Pulling" sensation in groin. |
| **Thecoma** | Benign. May produce estrogen. Usually presents as abnormal uterine bleeding in a postmenopausal female. |
| **Sertoli-Leydig cell tumor** | Benign. Small, grey to yellow-brown mass. Resembles testicular histology with tubules/cords lined by pink Sertoli cells. May produce androgens → virilization (eg, hirsutism, male pattern baldness, clitoral enlargement). |
| **Granulosa cell tumor** | Most common malignant sex cord stromal tumor. Predominantly occurs in females in their 50s. Often produces estrogen and/or progesterone. Presents with postmenopausal bleeding, endometrial hyperplasia, sexual precocity (in preadolescents), breast tenderness. Histology shows Call-Exner bodies (granulosa cells arranged haphazardly around collections of eosinophilic fluid, resembling primordial follicles; arrow in F). Tumor marker: ↑ inhibin. "Give Granny a Call." |

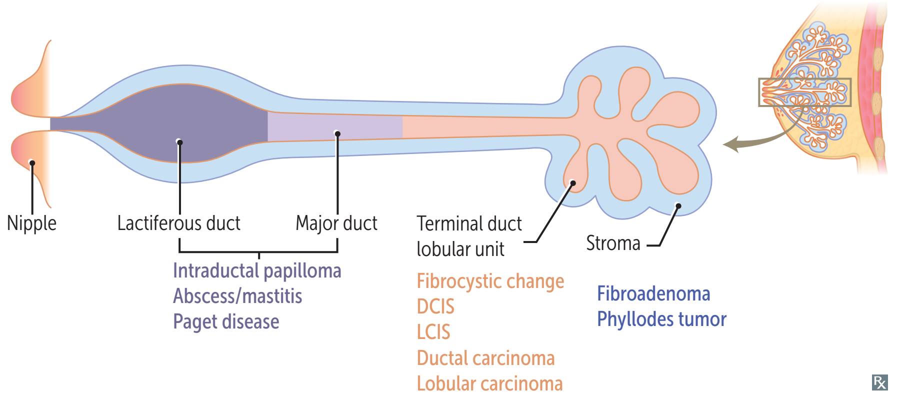


## Uterine conditions

| TYPE | CHARACTERISTICS |
|---|---|
| **Non-neoplastic uterine conditions** | |
| **Adenomyosis** | Extension of endometrial tissue (glandular) into uterine myometrium. Caused by hyperplasia of basal layer of endometrium. Presents with dysmenorrhea, AUB/HMB, and uniformly enlarged, soft, globular uterus. Treatment: GnRH agonists, hysterectomy, excision of an organized adenomyoma. |
| **Asherman syndrome** | Adhesions and/or fibrosis of the endometrium. Presents with ↓ fertility, recurrent pregnancy loss, AUB, pelvic pain. Often associated with dilation and curettage of intrauterine pregnancy. |
| **Endometrial hyperplasia** | Abnormal endometrial gland proliferation usually stimulated by excess estrogen. ↑ risk for endometrial carcinoma (especially with nuclear atypia). Presents as postmenopausal vaginal bleeding. ↑ risk with anovulatory cycles, hormone replacement therapy, PCOS, granulosa cell tumors. |
| **Endometriosis** | Endometrium-like glands/stroma outside endometrial cavity, most commonly in the ovary (frequently bilateral), pelvis, peritoneum (yellow-brown "powder burn" lesions). In ovary, appears as endometrioma (blood-filled "chocolate cysts" [oval structures above and below asterisks in A]). May be due to retrograde flow, metaplastic transformation of multipotent cells, transportation of endometrial tissue via lymphatic system. Characterized by cyclic pelvic pain, bleeding, dysmenorrhea, dyspareunia, dyschezia (pain with defecation), infertility; normal-sized uterus. Treatment: NSAIDs, OCPs, progestins, GnRH agonists, danazol, laparoscopic removal. |
| **Endometritis** | Inflammation of endometrium B associated with retained products of conception following delivery, miscarriage, abortion, or with foreign body (eg, IUD). Retained material is nidus for bacteria from vagina or GI tract. Chronic endometritis shows plasma cells on histology. Treatment: gentamicin + clindamycin +/– ampicillin. |
| **Uterine neoplasms** | |
| **Endometrial carcinoma** | Most common gynecologic malignancy. Presents with irregular vaginal bleeding. Two types:<br>Endometrioid C—most cases caused by unopposed estrogen exposure due to obesity, but also associated with early menarche, late menopause, nulliparity. Histology shows abnormally arranged endometrial glands. Early pathogenic events include loss of PTEN or mismatch repair proteins.<br>Serous—associated with endometrial atrophy in postmenopausal females. Aggressive. Psammoma bodies often seen on histology. Characterized by formation of papillae and tufts. |
| **Leiomyoma (fibroid)** | Most common tumor in females. Often presents with multiple discrete tumors D. ↑ incidence in Black patients. Benign smooth muscle tumor; malignant transformation to leiomyosarcoma is rare. Estrogen sensitive; tumor size ↑ with pregnancy and ↓ with menopause. Peak occurrence at 20-40 years of age. May be asymptomatic, cause AUB, or result in miscarriage. Severe bleeding may lead to iron deficiency anemia. Whorled pattern of smooth muscle bundles with well-demarcated borders on histology E. |
| **Leiomyosarcoma** | Malignant proliferation of smooth muscle arising from myometrium; arises de novo (not from leiomyomas), usually in postmenopausal females. Exam shows single lesion with areas of necrosis. |

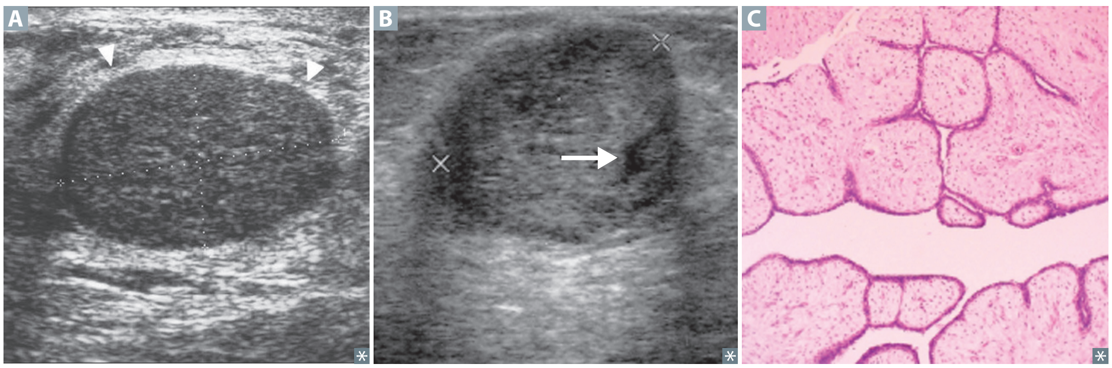


## Breast pathology

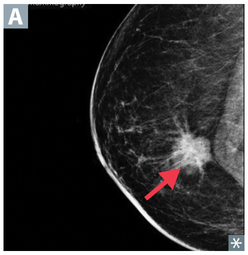



## Benign breast diseases

| | |
|---|---|
| **Fibrocystic changes** | Most common in premenopausal females 20-50 years old. Present with premenstrual breast pain or lumps; often bilateral and multifocal. Nonproliferative lesions include simple cysts (fluid-filled duct dilation, blue dome), papillary apocrine change/metaplasia, stromal fibrosis. Risk of cancer is usually not increased. Subtypes include:<br>▪ Sclerosing adenosis—acini and stromal fibrosis, associated with calcifications. Slight ↑ risk for cancer.<br>▪ Epithelial hyperplasia—cells in terminal ductal or lobular epithelium. ↑ risk of carcinoma with atypical cells. |
| **Inflammatory processes** | Fat necrosis—benign, usually painless, lump due to injury to breast tissue. Calcified oil cyst on mammography; necrotic fat and giant cells on biopsy. Up to 50% of patients may not report trauma.<br>Lactational mastitis—occurs during breastfeeding, ↑ risk of bacterial infection through cracks in nipple. *S aureus* is most common pathogen. Treat with antibiotics and continue breastfeeding. |
| **Benign tumors** | Fibroadenoma—most common in females < 35 years old. Small, well-defined, mobile mass A. Tumor composed of fibrous tissue and glands. ↑ size and tenderness with ↑ estrogen (eg, pregnancy, prior to menstruation). Risk of cancer is usually not increased.<br>Intraductal papilloma—small fibroepithelial tumor within lactiferous ducts, typically beneath areola. Most common cause of nipple discharge (serous or bloody). Slight ↑ risk for cancer.<br>Phyllodes tumor—large mass B of connective tissue and cysts with "leaf-like" lobulations C. Most common in 5th decade. Some may become malignant. |
| **Gynecomastia** | Breast enlargement in males due to ↑ estrogen compared with androgen activity. Physiologic in newborn, pubertal, and elderly males, but may persist after puberty. Other causes include cirrhosis, hypogonadism (eg, Klinefelter syndrome), testicular tumors, and drugs (spironolactone, hormones, cimetidine, finasteride, ketoconazole). |



## Breast cancer



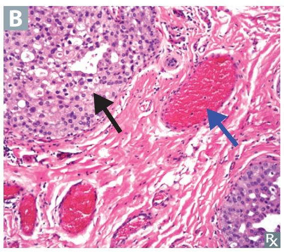
Commonly postmenopausal. Often presents as a palpable hard mass A most often in the upper outer quadrant. Invasive cancer can become fixed to pectoral muscles, deep fascia, Cooper ligaments, and overlying skin → nipple retraction/skin dimpling.

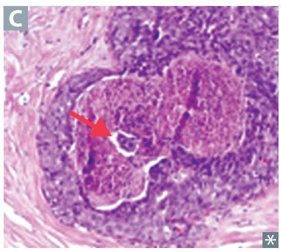
Usually arises from terminal duct lobular unit. Amplification/overexpression of estrogen/progesterone receptors or *c-erbB2* (HER2, an EGF receptor) is common; triple negative (ER ⊖, PR ⊖, and HER2/neu ⊖) form more aggressive.

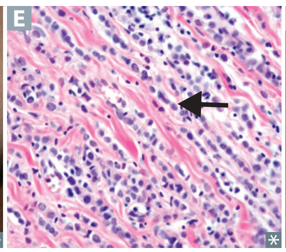
Risk factors in females: ↑ age; history of atypical hyperplasia; family history of breast cancer; race (White patients at highest risk, Black patients at ↑ risk for triple ⊖ breast cancer); *BRCA1/BRCA2* mutations; ↑ estrogen exposure (eg, nulliparity); postmenopausal obesity (adipose tissue converts androstenedione to estrone); ↑ total number of menstrual cycles; absence of breastfeeding; later age of first pregnancy; alcohol intake. In males: *BRCA2* mutation, Klinefelter syndrome.

Axillary lymph node metastasis most important prognostic factor in early-stage disease.

| TYPE | CHARACTERISTICS | NOTES |
|---|---|---|
| **Noninvasive carcinomas** | | |
| **Ductal carcinoma in situ** | Fills ductal lumen (black arrow in B indicates neoplastic cells in duct; blue arrow shows engorged blood vessel). Arises from ductal atypia. Often seen early as microcalcifications on mammography. | Early malignancy without basement membrane penetration. Usually does not produce a mass. Comedocarcinoma—Subtype of DCIS. Cells have high-grade nuclei with extensive central necrosis C and dystrophic calcification. |
| **Paget disease** | Extension of underlying DCIS/invasive breast cancer up the lactiferous ducts and into the contiguous skin of nipple → eczematous patches over nipple and areolar skin D. | Paget cells = intraepithelial adenocarcinoma cells. |
| **Lobular carcinoma in situ** | ↓ E-cadherin expression. No mass or calcifications → incidental biopsy finding. | ↑ risk of cancer in either breast (vs DCIS, same breast and quadrant). |
| **Invasive carcinomas[a]** | | |
| **Invasive ductal** | Firm, fibrous, "rock-hard" mass with sharp margins and small, glandular, duct-like cells in desmoplastic stroma. | Most common type of invasive breast cancer. |
| **Invasive lobular** | ↓ E-cadherin expression → orderly row of cells ("single file" E) and no duct formation. Often lacks desmoplastic response. | Often bilateral with multiple lesions in the same location. Lines of cells = Lobular. |
| **Medullary** | Large, anaplastic cells growing in sheets with associated lymphocytes and plasma cells. | Well-circumscribed tumor can mimic fibroadenoma. |
| **Inflammatory** | Dermal lymphatic space invasion → breast pain with warm, swollen, erythematous skin around exaggerated hair follicles (peau d'orange) F. | Poor prognosis (50% survival at 5 years). Often mistaken for mastitis or Paget disease. Usually lacks a palpable mass. |







[a]All types of invasive breast carcinoma can be either of tubular subtype (well-differentiated tubules that lack myoepithelium) or mucinous subtype (abundant extracellular mucin, seen in older females).

## Penile pathology

### Peyronie disease

Abnormal curvature of penis A due to fibrous plaque within tunica albuginea. Associated with repeated minor trauma during intercourse. Can cause pain, anxiety, erectile dysfunction. Consider surgical repair or treatment with collagenase injections once curvature stabilizes. Distinct from penile fracture (rupture of corpora cavernosa due to forced bending).

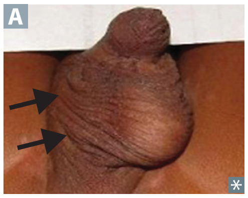
### Ischemic priapism

Painful sustained erection lasting > 4 hours. Associated with sickle cell disease (sickled RBCs block venous drainage of corpus cavernosum vascular channels), medications (eg, sildenafil, trazodone). Treat immediately with corporal aspiration, intracavernosal phenylephrine, or surgical decompression to prevent ischemia.

### Squamous cell carcinoma

Seen in the US, but more common in Asia, Africa, South America. Precursor in situ lesions: Bo**w**en disease (in penile shaft, presents as leukoplakia "**w**hite plaque"), erythroplasia of Quey**r**at (carcinoma in situ of the glans B, presents as erythroplakia "**r**ed plaque"), Bowenoid papulosis (carcinoma in situ of unclear malignant potential, presenting as reddish papules). Associated with uncircumcised males and HPV.

## Cryptorchidism



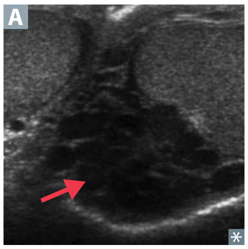
Descent failure of one A or both testes; impaired spermatogenesis (since sperm develop best at temperatures < 37°C); can have normal testosterone levels (Leydig cells are mostly unaffected by temperature); associated with $\uparrow$ risk of germ cell tumors. Prematurity $\uparrow$ risk of cryptorchidism. $\downarrow$ inhibin B, $\uparrow$ FSH, $\uparrow$ LH; testosterone $\downarrow$ in bilateral cryptorchidism, normal in unilateral. Most cases resolve spontaneously; otherwise, orchiopexy performed before 2 years of age.

## Testicular torsion

Rotation of testicle around spermatic cord and vascular pedicle. Commonly presents in males 12–18 years old. Associated with congenital horizontal positioning of testes ("bell clapper" deformity). May occur after an inciting event (eg, trauma) or spontaneously. Characterized by acute, severe pain, high-riding testis, and absent cremasteric reflex. $\ominus$ Prehn sign.

Treatment: surgical correction (orchiopexy) within 6 hours, manual detorsion if surgical option unavailable in timeframe. If testis is not viable, orchiectomy. Orchiopexy, when performed, should be bilateral because the contralateral testis is at risk for subsequent torsion.

## Varicocele



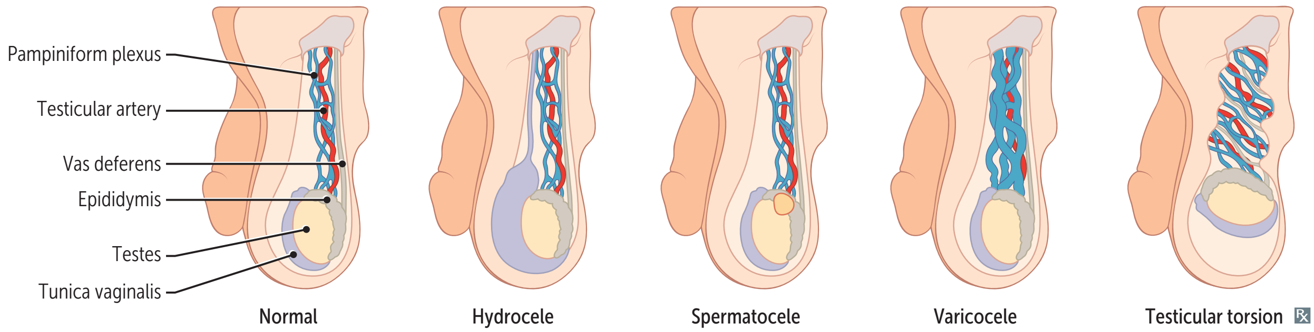
Dilated veins in pampiniform plexus due to $\uparrow$ venous pressure; most common cause of scrotal enlargement in adult males; most often on left side because of $\uparrow$ resistance to flow from left gonadal vein drainage into left renal vein; can cause infertility because of $\uparrow$ temperature; diagnosed by standing clinical exam/Valsalva maneuver (distension on inspection and "bag of worms" on palpation; augmented by Valsalva) or ultrasound A; does not transilluminate.

Treatment: consider surgical ligation or embolization if associated with pain or infertility.

| | |
|---|---|
| **Extragonadal germ cell tumors** | Arise in midline locations. In adults, most commonly in retroperitoneum, mediastinum, pineal, and suprasellar regions. In infants and young children, sacrococcygeal teratomas are most common. |

**Benign scrotal lesions** Testicular masses that can be transilluminated (vs solid testicular tumors).

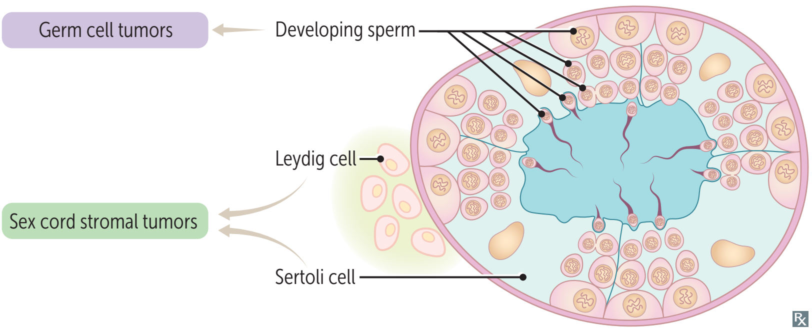
| | | |
|---|---|---|
| **Congenital hydrocele**  | Common cause of scrotal swelling A in infants, due to incomplete obliteration of processus vaginalis. Most spontaneously resolve within 1 year. | Communicating hydrocele. |
| **Acquired hydrocele** | Scrotal fluid collection usually 2° to infection, trauma, tumor. If bloody → hematocele. | Noncommunicating hydrocele. |
| **Spermatocele** | Cyst due to dilated epididymal duct or rete testis. | Paratesticular fluctuant nodule. |




**Testicular tumors**

Germ cell tumors account for ~ 95% of all testicular tumors. Arise from germ cells that produce sperm. Most often occur in young males. Risk factors: cryptorchidism, Klinefelter syndrome. Can present as a mixed germ cell tumor. Do not transilluminate. Usually not biopsied (risk of seeding scrotum), removed via radical orchiectomy.

Sex cord stromal tumors develop from embryonic sex cord (develops into Sertoli and Leydig cells of seminiferous tubules, theca and granulosa cells of follicle) derivatives. 5% of all testicular tumors. Mostly benign.



### Testicular tumors *(continued)*

| TYPE | CHARACTERISTICS |
|---|---|
| **Germ cell tumors** | |
| **Seminoma** | Malignant. Painless, homogenous testicular enlargement. Most common testicular tumor. Analogous to ovarian dysgerminoma. Does not occur in infancy. Large cells in lobules with watery cytoplasm and "fried egg" appearance on histology, ↑ placental ALP (PALP). Highly radiosensitive. Late metastasis, excellent prognosis. |
| **Embryonal carcinoma** | Malignant. Painful, hemorrhagic mass with necrosis. Often glandular/papillary morphology. "Pure" embryonal carcinoma is rare; most commonly mixed with other tumor types. May present with metastases. May be associated with ↑ hCG and normal AFP levels when pure (↑ AFP when mixed). Worse prognosis than seminoma. |
| **Teratoma** | **M**ature teratoma may be **m**alignant in adult **m**ales. Benign in children and females. |
| **Yolk sac tumor** | Also called endodermal sinus tumor. Malignant, aggressive. Yellow, mucinous. Analogous to ovarian yolk sac tumor. **S**chiller-Duval bodies resemble primitive glomeruli. ↑ **A**FP is highly characteristic. Most common testicular tumor in **c**hildren < 3 years old. |
| **Choriocarcinoma** | Malignant. Disordered syncytiotrophoblastic and cytotrophoblastic elements. Hematogenous metastases to lungs and brain. ↑ hCG. May produce gynecomastia, symptoms of hyperthyroidism (α-subunit of hCG is identical to α-subunit of LH, FSH, TSH). |
| **Non–germ cell tumors** | |
| **Leydig cell tumor** | Mostly benign. Golden brown color; contains Reinke crystals (eosinophilic cytoplasmic inclusions). Produces androgens or estrogens → precocious puberty, gynecomastia. |
| **Sertoli cell tumor** | Also called androbla**stoma** (arises from sex cord **stroma**). Mostly benign. |
| **Primary testicular lymphoma** | Malignant, aggressive. Typically diffuse large B-cell lymphoma. Most common testicular cancer in older males. |

### Hormone levels in germ cell tumors

| | SEMINOMA | YOLK SAC TUMOR | CHORIOCARCINOMA | TERATOMA | EMBRYONAL CARCINOMA |
|---|---|---|---|---|---|
| **PALP** | ↑ | – | – | – | – |
| **AFP** | – | ↑↑ | – | –/↑ | –/↑ (when mixed) |
| **β-hCG** | –/↑ | –/↑ | ↑↑ | – | ↑ |

**Epididymitis and orchitis**

Most common causes:
- *C trachomatis* and *N gonorrhoeae* (young males)
- *E coli* and *Pseudomonas* (older males, associated with UTI and BPH)
- Autoimmune (eg, granulomas involving seminiferous tubules)

**Epididymitis**

Inflammation of epididymis. Presents with localized pain and tenderness over posterior testis. ⊕ Prehn sign (pain relief with scrotal elevation). May progress to involve testis.

**Orchitis**

Inflammation of testis. Presents with testicular pain and swelling. Mumps orchitis ↑ infertility risk. Rare in males < 10 years old.

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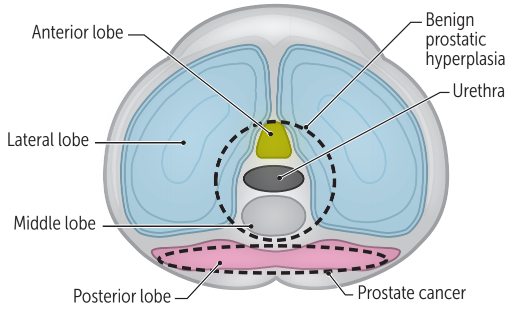
**Benign prostatic hyperplasia**

Common in males > 50 years old. Characterized by smooth, elastic, firm nodular enlargement (hyperplasia not hypertrophy) of periurethral (lateral and middle) lobes, which compress the urethra into a vertical slit. Not premalignant.

Often presents with ↑ frequency of urination, nocturia, difficulty starting and stopping urine stream, dysuria. May lead to distention and hypertrophy of bladder, hydronephrosis, UTIs. ↑ total PSA, with ↑ fraction of free PSA. PSA is made by prostatic epithelium stimulated by androgens.

Treatment: $\alpha_1$-antagonists (terazosin, tamsulosin), which cause relaxation of smooth muscle; 5α-reductase inhibitors (eg, finasteride); PDE-5 inhibitors (eg, tadalafil); surgical resection (eg, TURP, ablation).

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**Prostatitis**

Characterized by dysuria, frequency, urgency, low back pain. Warm, tender, enlarged prostate.

Acute bacterial prostatitis—in older males most common bacterium is *E coli*; in young males consider *C trachomatis*, *N gonorrhoeae*.

Chronic prostatitis—either bacterial or nonbacterial (eg, 2° to previous infection, nerve problems, chemical irritation).

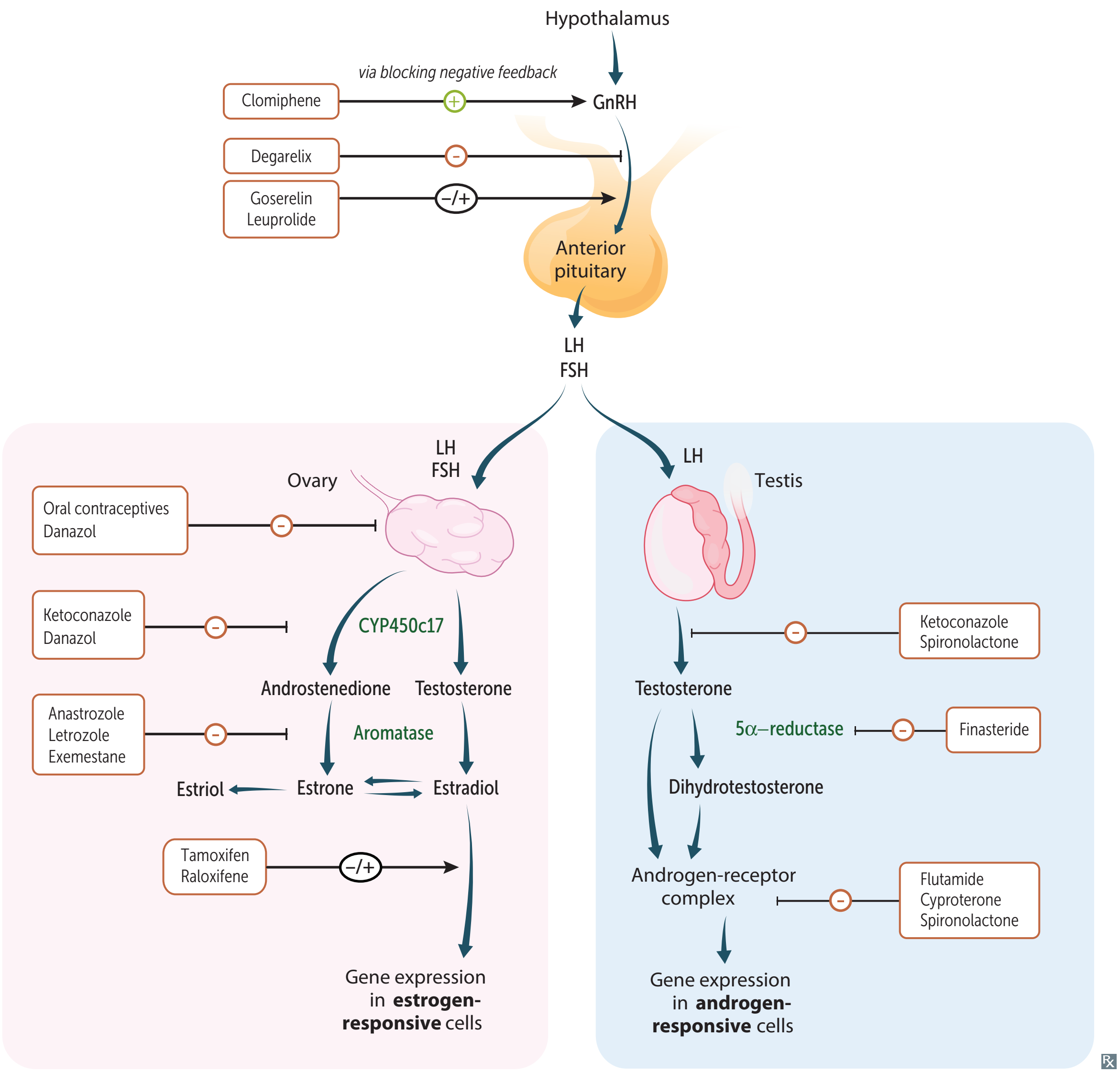
---

**Prostatic adenocarcinoma**

Common in males > 50 years old. Arises most often from posterior lobe (peripheral zone) of prostate gland and is most frequently diagnosed by ↑ PSA and subsequent needle core biopsies (transrectal, ultrasound-guided). Histologically graded using **Gl**eason grade, which is based on **gl**andular architecture and correlates closely with metastatic potential. Prostatic acid phosphatase (PAP) and PSA are useful tumor markers (↑ total PSA, with ↓ fraction of free PSA). Osteoblastic metastases in bone may develop in late stages, as indicated by lower back pain and ↑ serum ALP and PSA. Metastasis to the spine often occurs via Batson (vertebral) venous plexus.

## ▶ REPRODUCTIVE—PHARMACOLOGY

### Control of reproductive hormones



| | |
|---|---|
| **Gonadotropin-releasing hormone analogs** | **Leu**prolide, goserelin, nafarelin, histrelin. |
| MECHANISM | Act as GnRH agonists when used in pulsatile fashion.<br>When used in continuous fashion, first transiently act as GnRH agonists (tumor flare), but subsequently act as GnRH antagonists (downregulate GnRH receptor in pituitary → ↓ FSH and ↓ LH).<br>Can be used in **lieu** of GnRH. |
| CLINICAL USE | Uterine fibroids, endometriosis, precocious puberty, prostate cancer, infertility. **P**ulsatile for **p**regnancy, **c**ontinuous for **c**ancer. |
| ADVERSE EFFECTS | Hypogonadism, ↓ libido, erectile dysfunction, nausea, vomiting. |

| | |
|---|---|
| **Degarelix** | |
| MECHANISM | GnRH antagonist. No start-up flare. |
| CLINICAL USE | Prostate cancer. |
| ADVERSE EFFECTS | Hot flashes, liver toxicity. |

| | |
|---|---|
| **Estrogens** | Ethinyl estradiol, DES, mestranol. |
| MECHANISM | Bind estrogen receptors. |
| CLINICAL USE | Hypogonadism or ovarian failure, menstrual abnormalities (combined OCPs), hormone replacement therapy in postmenopausal females. |
| ADVERSE EFFECTS | ↑ risk of endometrial cancer (when given without progesterone), bleeding in postmenopausal patients, clear cell adenocarcinoma of vagina in females exposed to DES in utero, ↑ risk of thrombi. Contraindications—ER ⊕ breast cancer, history of DVTs, tobacco use in females > 35 years old. |

| | |
|---|---|
| **Selective estrogen receptor modulators** | |
| **Clomiphene** | Antagonist at estrogen receptors in hypothalamus. Prevents normal feedback inhibition and ↑ release of LH and FSH from pituitary, which stimulates ovulation. Used to treat infertility due to anovulation (eg, PCOS). May cause hot flashes, ovarian enlargement, multiple simultaneous pregnancies, visual disturbances. |
| **Tamoxifen** | Antagonist at breast, partial agonist at uterus, bone. Hot flashes, ↑ risk of thromboembolic events (especially with tobacco smoking), and endometrial cancer. Used to treat and prevent recurrence of ER/PR ⊕ breast cancer and to prevent gynecomastia in patients undergoing prostate cancer therapy. |
| **Raloxifene** | Antagonist at breast, uterus; agonist at bone; hot flashes, ↑ risk of thromboembolic events (especially with tobacco smoking), but no increased risk of endometrial cancer (vs tamoxifen, so you can "**relax**"); used primarily to treat osteoporosis. |

| | |
|---|---|
| **Aromatase inhibitors** | Anastrozole, letrozole, exemestane. |
| MECHANISM | Inhibit peripheral conversion of androgens to estrogen. |
| CLINICAL USE | ER ⊕ breast cancer in postmenopausal females. |

| | |
|---|---|
| **Hormone replacement therapy** | Used for relief or prevention of menopausal symptoms (eg, hot flashes, vaginal atrophy), osteoporosis (↑ estrogen, ↓ osteoclast activity).<br>Unopposed estrogen replacement therapy ↑ risk of endometrial cancer, progesterone/progestin is added. Possible increased cardiovascular risk. |

| | |
|---|---|
| **Progestins** | Levonorgestrel, medroxyprogesterone, etonogestrel, norethindrone, megestrol. |
| MECHANISM | Bind progesterone receptors, ↓ growth and ↑ vascularization of endometrium, thicken cervical mucus. |
| CLINICAL USE | Contraception (forms include pill, intrauterine device, implant, depot injection), endometrial cancer, abnormal uterine bleeding. Progestin challenge: presence of bleeding upon withdrawal of progestins excludes anatomic defects (eg, Asherman syndrome) and chronic anovulation without estrogen. |

| | |
|---|---|
| **Antiprogestins** | Mifepristone, ulipristal. |
| MECHANISM | Competitive inhibitors of progestins at progesterone receptors. |
| CLINICAL USE | Termination of pregnancy (mifepristone with misoprostol); emergency contraception (ulipristal). |

| | |
|---|---|
| **Combined contraception** | Progestins and ethinyl estradiol; forms include pill, patch, vaginal ring.<br>Estrogen and progestins inhibit LH/FSH and thus prevent estrogen surge. No estrogen surge → no LH surge → no ovulation.<br>Progestins cause thickening of cervical mucus, thereby limiting access of sperm to uterus. Progestins also inhibit endometrial proliferation → endometrium is less suitable to the implantation of an embryo.<br>Adverse effects: breakthrough menstrual bleeding, breast tenderness, VTE, hepatic adenomas.<br>Contraindications: people > 35 years old who smoke tobacco (↑ risk of cardiovascular events), patients with ↑ risk of cardiovascular disease (including history of venous thromboembolism, coronary artery disease, stroke), migraine (especially with aura), breast cancer, liver disease. |

| **Copper intrauterine device** | |
|---|---|
| MECHANISM | Produces local inflammatory reaction toxic to sperm and ova, preventing fertilization and implantation; hormone free. |
| CLINICAL USE | Long-acting reversible contraception. Most effective emergency contraception. |
| ADVERSE EFFECTS | Heavier or longer menses, dysmenorrhea. Insertion contraindicated in active PID (IUD may impede PID resolution). |

| | |
|---|---|
| **Tocolytics** | Medications that relax the uterus; include terbutaline ($\beta_2$-agonist action), nifedipine ($Ca^{2+}$ channel blocker), indomethacin (NSAID). Used to ↓ contraction frequency in preterm labor and allow time for administration of steroids (to promote fetal lung maturity) or transfer to appropriate medical center with obstetrical care. |

## Danazol

| | |
|---|---|
| MECHANISM | Synthetic androgen that acts as partial agonist at androgen receptors. |
| CLINICAL USE | Endometriosis, hereditary angioedema. |
| ADVERSE EFFECTS | Weight gain, edema, acne, hirsutism, masculinization, ↓ HDL levels, hepatotoxicity, idiopathic intracranial hypertension. |

## Testosterone, methyltestosterone

| | |
|---|---|
| MECHANISM | Agonists at androgen receptors. |
| CLINICAL USE | Treat hypogonadism and promote development of 2° sex characteristics; stimulate anabolism to promote recovery after burn or injury. |
| ADVERSE EFFECTS | Masculinization in females; ↓ intratesticular testosterone in males by inhibiting release of LH (via negative feedback) → gonadal atrophy. Premature closure of epiphyseal plates. ↑ LDL, ↓ HDL. |

## Antiandrogens

| DRUG | MECHANISM | CLINICAL USE | ADVERSE EFFECTS |
|---|---|---|---|
| **Abiraterone** | 17α-hydroxylase/17,20-lyase inhibitor (↓ steroid synthesis) | Prostate cancer | Hypertension, hypokalemia (↑ mineralocorticoids) |
| **Finasteride** | 5α-reductase inhibitor (↓ conversion of testosterone to DHT) | BPH, male-pattern baldness | Gynecomastia, sexual dysfunction |
| **Flutamide, bicalutamide** | Nonsteroidal competitive inhibitors at androgen receptor (↓ steroid binding) | Prostate cancer | Gynecomastia, sexual dysfunction |
| **Ketoconazole** | 17α-hydroxylase/17,20-lyase inhibitor | Prostate cancer | Gynecomastia |
| **Spironolactone** | Androgen receptor and 17α-hydroxylase/17,20-lyase inhibitor | PCOS | Amenorrhea |

## Tamsulosin

$\alpha_1$-antagonist used to treat BPH by inhibiting smooth muscle contraction. Selective for $\alpha_{1A/D}$ receptors (found on prostate) vs vascular $\alpha_{1B}$ receptors.

## Minoxidil

| | |
|---|---|
| MECHANISM | Direct arteriolar vasodilator. |
| CLINICAL USE | Androgenetic alopecia (pattern baldness), severe refractory hypertension. |

# Respiratory

*"There's so much pollution in the air now that if it weren't for our lungs, there'd be no place to put it all."*

—Robert Orben

*"Freedom is the oxygen of the soul."*

—Moshe Dayan

*"Whenever I feel blue, I start breathing again."*

—L. Frank Baum

*"Life is not the amount of breaths you take; it's the moments that take your breath away."*

—Will Smith, *Hitch*

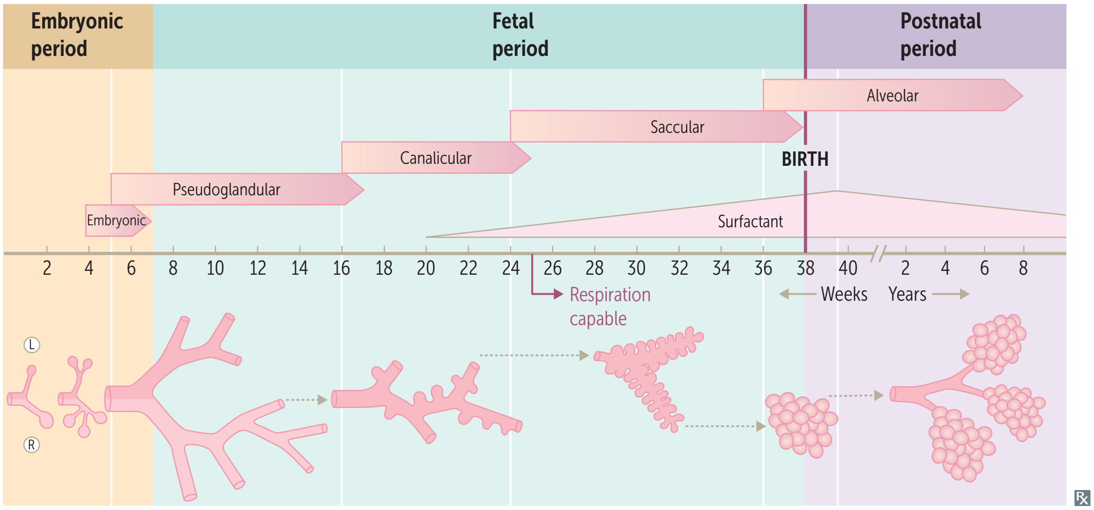
Group key respiratory, cardiovascular, and renal concepts together for study whenever possible. Respiratory physiology is challenging but high yield, especially as it relates to the pathophysiology of respiratory diseases. Develop a thorough understanding of normal respiratory function. Know obstructive vs restrictive lung disorders, $\dot{V}/\dot{Q}$ mismatch, lung volumes, mechanics of respiration, and hemoglobin physiology. Lung cancers and other causes of lung masses are also high yield. Be comfortable reading basic chest x-rays, CT scans, and PFTs.

## ▶ RESPIRATORY—EMBRYOLOGY

### Lung development

Occurs in five stages. Begins with the formation of lung bud from distal end of respiratory diverticulum during week 4 of development. Every pulmonologist can see alveoli.

| STAGE | STRUCTURAL DEVELOPMENT | NOTES |
|---|---|---|
| **Embryonic (weeks 4–7)** | Lung bud → trachea → bronchial buds → mainstem bronchi → secondary (lobar) bronchi → tertiary (segmental) bronchi. | Errors at this stage can lead to tracheoesophageal fistula. |
| **Pseudoglandular (weeks 5–17)** | Endodermal tubules → terminal bronchioles. Surrounded by modest capillary network. | Respiration impossible, incompatible with life. |
| **Canalicular (weeks 16–25)** | Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network. | Airways increase in diameter. Pneumocytes develop starting at week 20 of development. Respiration capable at ~ week 25. |
| **Saccular (week 24–birth)** | Alveolar ducts → terminal sacs. Terminal sacs separated by 1° septae. | |
| **Alveolar (week 36–8 years)** | Terminal sacs → adult alveoli (due to 2° septation).<br>In utero, "breathing" occurs via aspiration and expulsion of amniotic fluid → ↑ pulmonary vascular resistance through gestation.<br>At birth, air replaces fluid → ↓ pulmonary vascular resistance. | |




### Congenital lung malformations

| | |
|---|---|
| **Pulmonary hypoplasia** | Poorly developed bronchial tree with abnormal histology. Associated with congenital diaphragmatic hernia (usually left-sided), bilateral renal agenesis (Potter sequence). |
| **Bronchogenic cysts** | Caused by abnormal budding of the foregut and dilation of terminal or large bronchi. Discrete, round, sharply defined, fluid-filled densities on CXR (air-filled if infected). Generally asymptomatic but can drain poorly → airway compression, recurrent respiratory infections. |

**Club cells**

Nonciliated; low columnar/cuboidal with secretory granules. Located in bronchioles. Degrade toxins via cytochrome P-450; secrete component of surfactant; progenitor cells for club and ciliated cells.

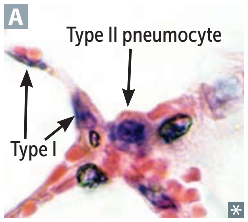
## Alveolar cell types

**Type I pneumocytes**

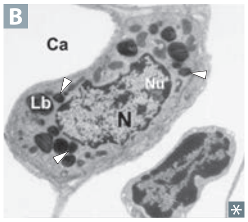
Squamous. 97% of alveolar surfaces. Thinly line the alveoli (two black arrows in A) for optimal gas exchange.

**Type II pneumocytes**

A




B




Cuboidal and clustered A.

2 functions:

1. Serve as stem cell precursors for 2 cell types (type I and type II cells); proliferate during lung damage.
2. Secrete surfactant from lamellar bodies (arrowheads in B).

Surfactant— ↓ alveolar surface tension, ↓ alveolar collapse, ↓ lung recoil, and ↑ compliance.

Composed of multiple lecithins, mainly dipalmitoylphosphatidylcholine (DPPC).

Synthesis begins ~20 weeks' gestation and achieves mature levels ~35 weeks of gestation.

Corticosteroids important for fetal surfactant synthesis and lung development.

Collapsing pressure $(P) = \dfrac{2\ (\text{surface tension})}{\text{radius}}$

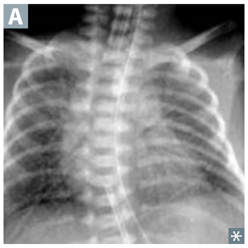
Law of Laplace—Alveoli have ↑ tendency to collapse on expiration as radius ↓.

**Alveolar macrophages**

Phagocytose foreign materials; release cytokines and alveolar proteases. Hemosiderin-laden macrophages (heart failure cells) may be found in the setting of pulmonary edema or alveolar hemorrhage.

## Neonatal respiratory distress syndrome

A



Surfactant deficiency → ↑ surface tension → alveolar collapse ("ground-glass" appearance of lung fields) A.

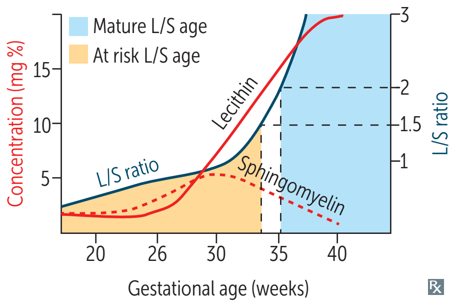
Risk factors: prematurity, diabetes during pregnancy (due to ↑ fetal insulin), C-section delivery (↓ release of fetal glucocorticoids; less stressful than vaginal delivery).

Treatment: maternal steroids before birth; exogenous surfactant for infant.

Therapeutic supplemental $O_2$ can result in **R**etinopathy of prematurity, **I**ntraventricular hemorrhage, **B**ronchopulmonary dysplasia (**RIB**).

Screening tests for fetal lung maturity: lecithin-sphingomyelin (L/S) ratio in amniotic fluid (≥ 2 is healthy; < 1.5 predictive of NRDS), foam stability index, surfactant-albumin ratio.

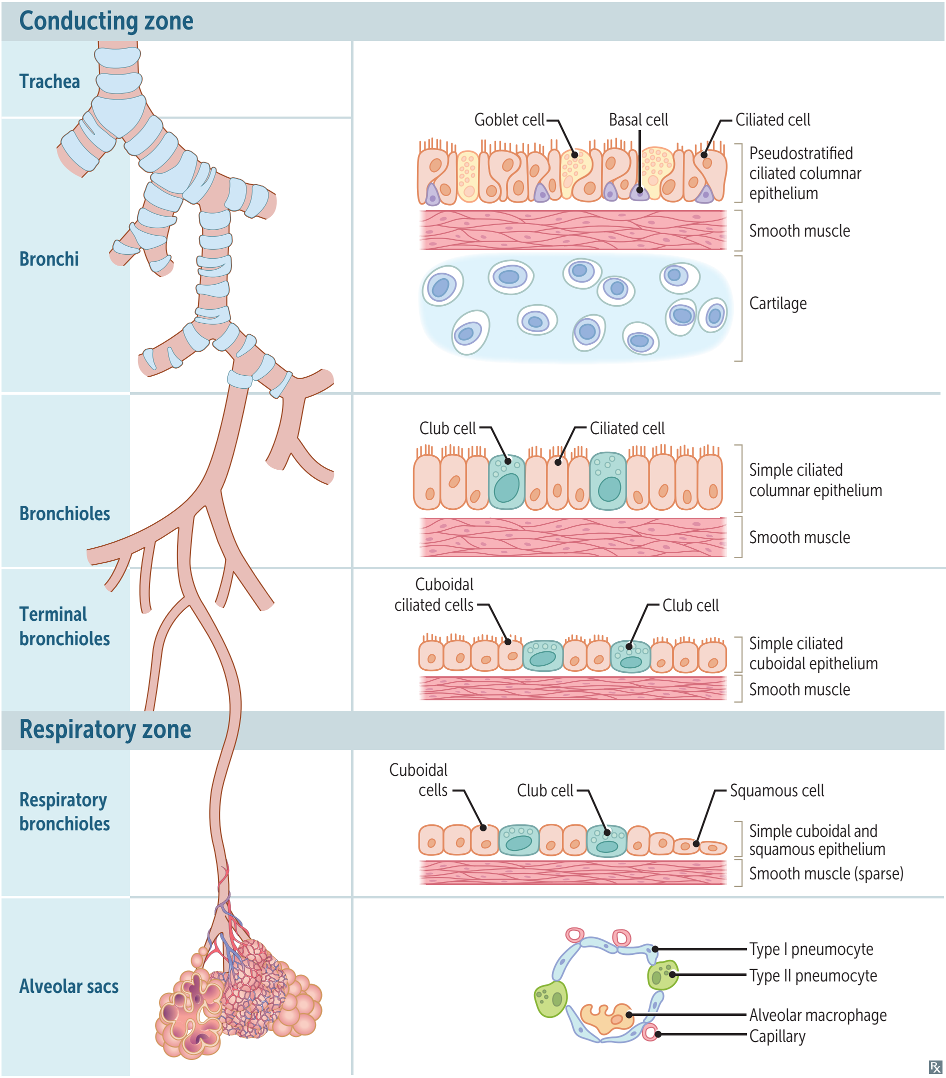
Persistently low $O_2$ tension → risk of PDA.



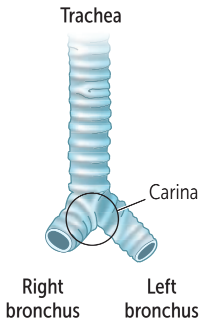
## ▸ RESPIRATORY—ANATOMY

### Respiratory tree

| | |
|---|---|
| **Conducting zone** | Large airways consist of nose, pharynx, larynx, trachea, and bronchi. Airway resistance highest in the large- to medium-sized bronchi. Small airways consist of bronchioles that further divide into terminal bronchioles (large numbers in parallel → least airway resistance).<br>Warms, humidifies, and filters air but does not participate in gas exchange → "anatomic dead space."<br>Cartilage and goblet cells extend to the end of bronchi.<br>Pseudostratified ciliated columnar cells primarily make up epithelium of bronchus and extend to beginning of terminal bronchioles, then transition to cuboidal cells. Clear mucus and debris from lungs (mucociliary escalator).<br>Airway smooth muscle cells extend to end of terminal bronchioles (sparse beyond this point). |
| **Respiratory zone** | Lung parenchyma; consists of respiratory bronchioles, alveolar ducts, and alveoli. Participates in gas exchange.<br>Mostly cuboidal cells in respiratory bronchioles, then simple squamous cells up to alveoli. Cilia terminate in respiratory bronchioles. Alveolar macrophages clear debris and participate in immune response. |



## Lung anatomy

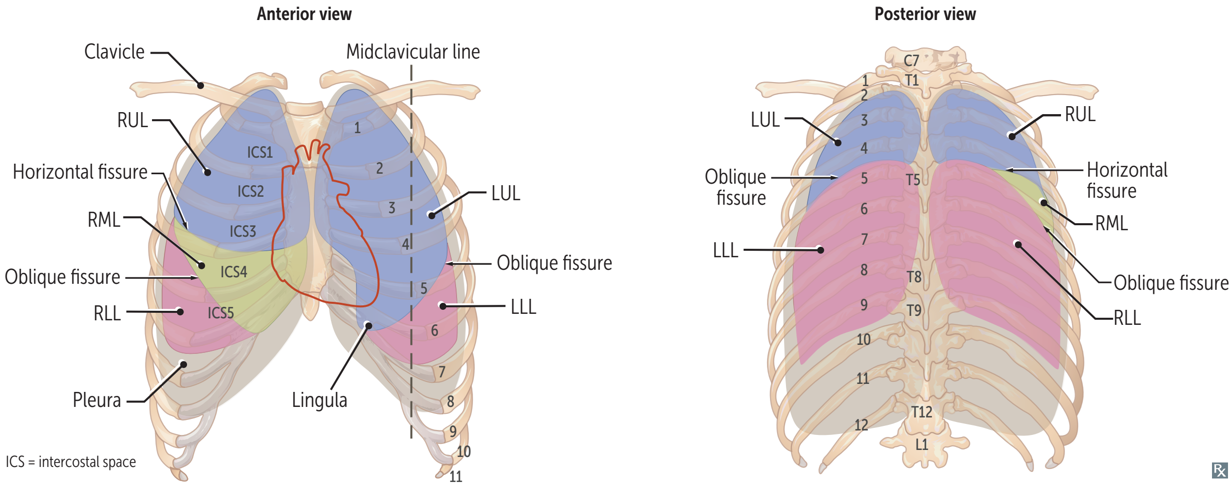


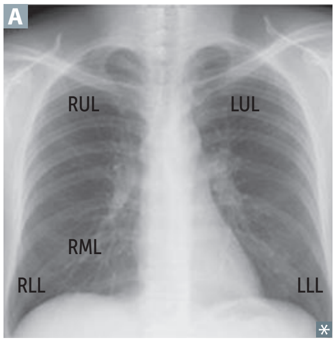

Right lung has 3 lobes; **L**eft has **l**ess **l**obes (2) and **l**ingula (homolog of right middle lobe). Instead of a middle lobe, left lung has a space occupied by the heart **A**.

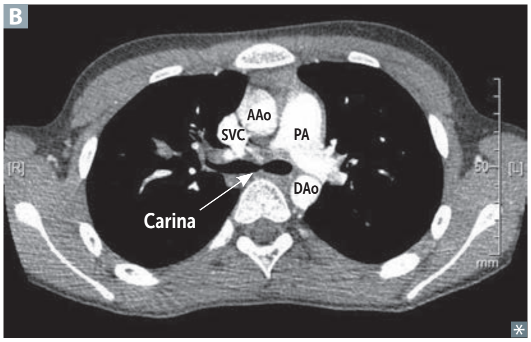
Relation of the pulmonary artery to the bronchus at each lung hilum is described by **RALS**—**R**ight **A**nterior; **L**eft **S**uperior. Carina is posterior to ascending aorta and anteromedial to descending aorta **B**.

Right lung is a more common site for inhaled foreign bodies because right main stem bronchus is wider, more vertical, and shorter than the left. If you aspirate a peanut:

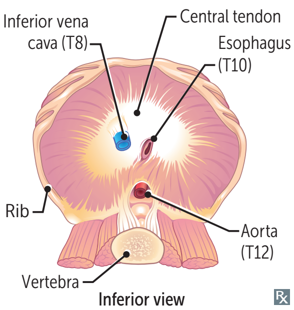
- While supine—usually enters superior segment of right lower lobe.
- While lying on right side—usually enters right upper lobe.
- While upright—usually enters right lower lobe.




## Diaphragm structures




Structures perforating diaphragm:

- At T8: IVC, right phrenic nerve
- At T**10**: esophagus, vagus (CN **10**; 2 trunks)
- At T12: aorta (red), thoracic duct (white), azygos vein (blue) ("At **T-1-2** it's the **red**, **white**, and **blue**")

Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from diaphragm irritation (eg, air, blood, or pus in peritoneal cavity) can be referred to shoulder (C5) and trapezius ridge (C3, 4).

Number of letters = T level:

T**8**: vena cava (**I**VC)
T**10**: (O)**esophagus**
T**12**: **aort**ic hiatus

**I** ate (8) **ten eggs at twelve**.

**C3**, **4**, **5** keeps the diaphragm **alive**.

Other bifurcations:

- The **C**ommon **C**arotid bi**four**cates at **C4**.
- The **T**rachea bi**four**cates at **T4**.
- The abdominal aorta bi**four**cates at L**4**.

## ▸ RESPIRATORY—PHYSIOLOGY

### Lung volumes and capacities

Note: a capacity is a sum of ≥ 2 physiologic volumes.

**Tidal volume** — Air that moves into lung with each quiet inspiration, typically 500 mL

**Inspiratory reserve volume** — Air that can still be breathed in after normal inspiration

**Expiratory reserve volume** — Air that can still be breathed out after normal expiration

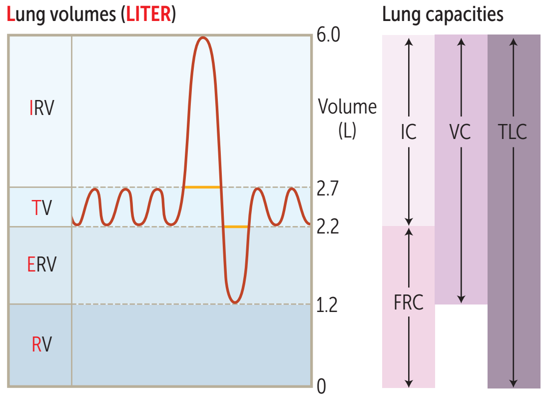
**Residual volume** — Air in lung after maximal expiration; RV and any lung capacity that includes RV cannot be measured by spirometry

**Inspiratory capacity** — IRV + TV
Air that can be breathed in after normal exhalation

**Functional residual capacity** — RV + ERV
Volume of gas in lungs after normal expiration; outward pulling force of chest wall is balanced with inward collapsing force of lungs

**Vital capacity** — IRV + TV + ERV
Maximum volume of gas that can be expired after a maximal inspiration

**Total lung capacity** — IRV + TV + ERV + RV = VC + RV
Volume of gas present in lungs after a maximal inspiration




IRV = inspiratory reserve volume
TV = tidal volume
ERV = expiratory reserve volume
RV = residual volume
IC = inspiratory capacity
FRC = functional residual capacity
VC = vital capacity
TLC = total lung capacity

### Determination of physiologic dead space

$$V_D = V_T \times \frac{Pa_{CO_2} - Pe_{CO_2}}{Pa_{CO_2}}$$

$V_D$ = physiologic dead space = anatomic dead space of conducting airways plus alveolar dead space; apex of healthy lung is largest contributor of alveolar dead space. Volume of inspired air that does not take part in gas exchange.
$V_T$ = tidal volume.
$Pa_{CO_2}$ = arterial $P_{CO_2}$.
$Pe_{CO_2}$ = expired air $P_{CO_2}$.

Physiologic dead space—approximately equivalent to anatomic dead space in normal lungs. May be greater than anatomic dead space in lung diseases with $\dot{V}/\dot{Q}$ mismatch.

### Ventilation

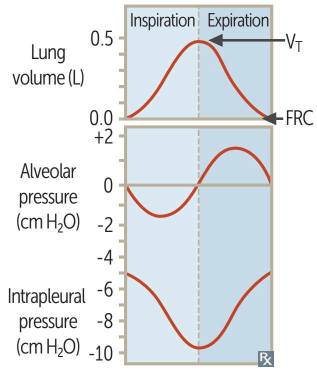
**Minute ventilation** — Abbreviated as $V_E$. Total volume of gas entering lungs per minute
$V_E = V_T \times RR$

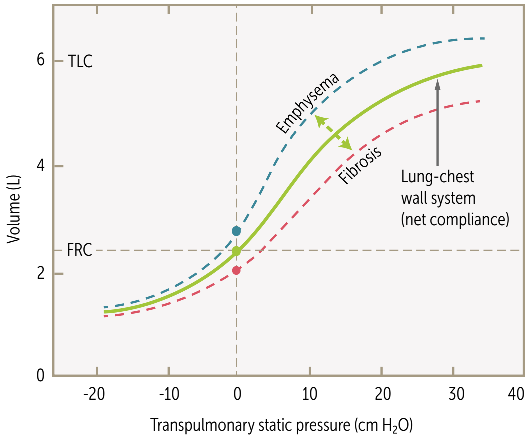
**Alveolar ventilation** — Abbreviated as $V_A$. Volume of gas that reaches alveoli each minute
$V_A = (V_T - V_D) \times RR$

Normal values:
- Respiratory rate (RR) = 12–20 breaths/min
- $V_T$ = 500 mL/breath
- $V_D$ = 150 mL/breath

## Lung and chest wall

| | |
|---|---|
| **Elastic recoil** | Tendency for lungs to collapse inward and chest wall to spring outward. At FRC, airway and alveolar pressures equal atmospheric pressure (called zero), and intrapleural pressure is negative (preventing atelectasis). The inward pull of the lung is balanced by the outward pull of the chest wall. System pressure is atmospheric. Pulmonary vascular resistance (PVR) is at a minimum. |
| **Compliance** | Change in lung volume for a change in pressure ($\Delta V/\Delta P$). Inversely proportional to wall stiffness and increased by surfactant.<br>▪ ↑ compliance = lung easier to fill (eg, emphysema, aging)<br>▪ ↓ compliance = lung harder to fill (eg, pulmonary fibrosis, pneumonia, ARDS, pulmonary edema) |
| **Hysteresis** | Lung inflation follows a different pressure-volume curve than lung deflation due to need to overcome surface tension forces in inflation. |



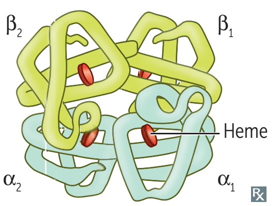




## Respiratory system changes in the elderly

Aging is associated with progressive ↓ in lung function. TLC remains the same.

| INCREASED | DECREASED |
|---|---|
| Lung compliance (loss of elastic recoil) | Chest wall compliance (↑ chest wall stiffness) |
| RV | FVC and $FEV_1$ |
| $\dot{V}/\dot{Q}$ mismatch | Respiratory muscle strength (can impair cough) |
| A-a gradient | Ventilatory response to hypoxia/hypercapnia |

## Hemoglobin




Normal adult hemoglobin (Hb) is composed of 4 polypeptide subunits (2 α and 2 β) that each bind one $O_2$ molecule. Hb is an allosteric protein that exhibits positive cooperativity when binding to $O_2$, such that:

- Oxygenated Hb has high affinity for $O_2$ (300×).
- Deoxygenated Hb has low affinity for $O_2$ → promotes release/unloading of $O_2$.

The protein component of hemoglobin acts as buffer for $H^+$ ions.

Myoglobin is composed of a single polypeptide chain associated with one heme moiety. Higher affinity for oxygen than Hb.

## Oxygen content of blood

$O_2$ content = (1.34 × Hb × $Sao_2$) + (0.003 × $Pao_2$).
Hb = hemoglobin concentration; $Sao_2$ = arterial $O_2$ saturation.
$Pao_2$ = partial pressure of $O_2$ in arterial blood.

Normally 1 g Hb can bind 1.34 mL $O_2$; normal Hb amount in blood is 15 g/dL.
$O_2$ binding capacity ≈ 20 mL $O_2$/dL of blood.
With ↓ Hb there is ↓ $O_2$ content of arterial blood, but no change in $O_2$ saturation and $Pao_2$.
$O_2$ delivery to tissues = cardiac output × $O_2$ content of blood.

| | Hb CONCENTRATION | % $O_2$ SAT OF Hb | DISSOLVED $O_2$ ($Pao_2$) | TOTAL $O_2$ CONTENT |
|---|---|---|---|---|
| CO poisoning | Normal | ↓ (CO competes with $O_2$) | Normal | ↓ |
| Anemia | ↓ | Normal | Normal | ↓ |
| Polycythemia | ↑ | Normal | Normal | ↑ |
| Methemoglobinemia | Normal | ↓ ($Fe^{3+}$ poor at binding $O_2$) | Normal | ↓ |
| Cyanide toxicity | Normal | Normal | Normal | Normal |

## Methemoglobin

Iron in Hb is normally in a reduced state (ferrous $Fe^{2+}$; "just the 2 of us"). Oxidized form of Hb (ferric, $Fe^{3+}$) does not bind $O_2$ as readily as $Fe^{2+}$, but has ↑ affinity for cyanide → tissue hypoxia from ↓ $O_2$ saturation and ↓ $O_2$ content.

Methemoglobinemia may present with cyanosis (does not improve with supplemental $O_2$) or with chocolate-colored blood.

Dapsone, local anesthetics (eg, benzocaine), and nitrites (eg, from dietary intake or polluted/high-altitude water sources) cause poisoning by oxidizing $Fe^{2+}$ to $Fe^{3+}$.

Methemoglobinemia can be treated with methylene blue and vitamin C.

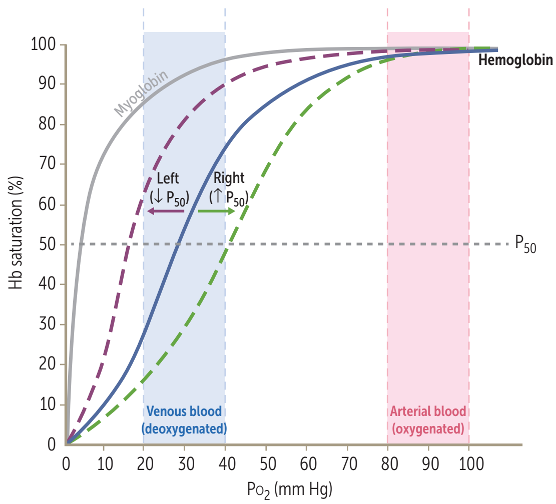
## Oxygen-hemoglobin dissociation curve

ODC has sigmoidal shape due to positive cooperativity (ie, tetrameric Hb molecule can bind 4 $O_2$ molecules and has higher affinity for each subsequent $O_2$ molecule bound). Myoglobin is monomeric and thus does not show positive cooperativity; curve lacks sigmoidal appearance.

Shifting ODC to the right → ↓ Hb affinity for $O_2$ (facilitates unloading of $O_2$ to tissue) → ↑ $P_{50}$ (higher $Po_2$ required to maintain 50% saturation). In peripheral tissue, ↑ $H^+$ from tissue metabolism shifts curve to right, unloading $O_2$ (Bohr effect).

Shifting ODC to the left → ↓ $O_2$ unloading → renal hypoxia → ↑ EPO synthesis → compensatory erythrocytosis.

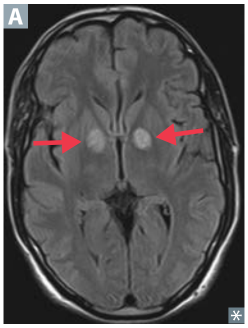
Fetal Hb (2 α and 2 γ subunits) has higher affinity for $O_2$ than adult Hb (due to ↓ affinity for 2,3-BPG) → dissociation curve is shifted left, driving diffusion of $O_2$ across the placenta from pregnant patient to fetus.

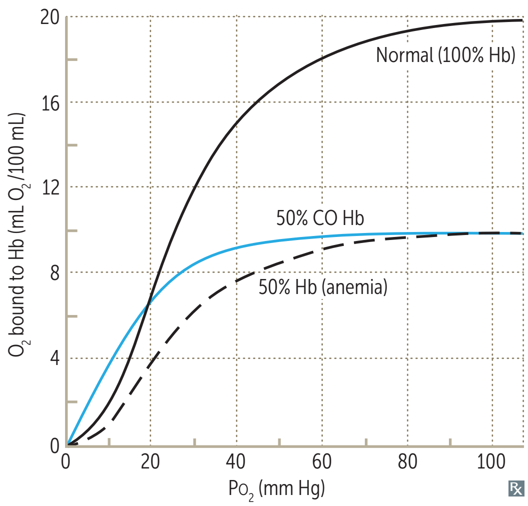



| Left shift (↓ $O_2$ unloading to tissue) Left = lower | Right shift (↑ $O_2$ unloading to tissues) ACE BATs right handed |
|---|---|
| ↓ $H^+$ (↑ pH, base) | ↑ $H^+$ (↓ pH, Acid) |
| ↓ $Pco_2$ | ↑ $Pco_2$ |
| ↓ 2,3-BPG | Exercise |
| ↓ Temperature | ↑ 2,3-BPG |
| ↑ CO | High Altitude |
| ↑ MetHb | ↑ Temperature |
| ↑ HbF | |

## Cyanide vs carbon monoxide poisoning

Both inhibit aerobic metabolism via inhibition of complex IV of ETC (cytochrome c oxidase) → hypoxia that does not fully correct with supplemental $O_2$ and ↑ anaerobic metabolism.

| | Cyanide | Carbon monoxide |
|---|---|---|
| EXPOSURE | Synthetic product combustion, amygdalin ingestion (found in apricot seeds), cyanide ingestion (eg, in suicide attempts), fire victims. | Motor exhaust, gas heaters, fire victims. |
| PRESENTATION | Headache, dyspnea, drowsiness, seizure, coma. May have cherry red skin. Breath may have bitter almond odor. | Headache, vomiting, confusion, visual disturbances, coma. May have cherry-red skin with bullous skin lesions. Multiple victims may be involved (eg, family due to faulty furnace). |
| LABS  | Normal $PaO_2$. Elevated lactate → metabolic acidosis. | Normal $PaO_2$. Elevated carboxyhemoglobin on co-oximetry. Classically associated with bilateral globus pallidus lesions on MRI A, although can rarely be seen with cyanide toxicity. |
| EFFECT ON OXYGEN-HEMOGLOBIN CURVE | Curve normal. Oxygen saturation may appear normal initially. Despite ample $O_2$ supply, it cannot be used due to ineffective oxidative phosphorylation. | Left shift in curve → ↑ affinity for $O_2$ → ↓ $O_2$ unloading in tissues. Binds competitively to Hb with > 200× greater affinity than $O_2$ to form carboxyhemoglobin → ↓ %$O_2$ saturation of Hb. |
| TREATMENT | Decontamination (eg, remove clothing). Hydroxocobalamin (binds cyanide → cyanocobalamin → renal excretion). Nitrites (oxidize Hb → methemoglobin → binds cyanide → cyanomethemoglobin → ↓ toxicity). Sodium thiosulfate (↑ cyanide conversion to thiocyanate → renal excretion). | 100% $O_2$. Hyperbaric oxygen if severe. |



### Pulmonary circulation

Normally a low-resistance, high-compliance system. A ↓ in $P_{AO_2}$ causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

Perfusion limited—$O_2$ (normal health), $CO_2$, $N_2O$. Gas equilibrates early along the length of the capillary. Exchange can be ↑ only if blood flow ↑.

Diffusion limited—$O_2$ (emphysema, fibrosis, exercise), CO. Gas does not equilibrate by the time blood reaches the end of the capillary.

$O_2$ diffuses slowly, while $CO_2$ diffuses very rapidly across the alveolar membrane. Disease states that lead to diffusion limitation (eg, pulmonary fibrosis) are more likely to cause early hypoxia than hypercapnia.

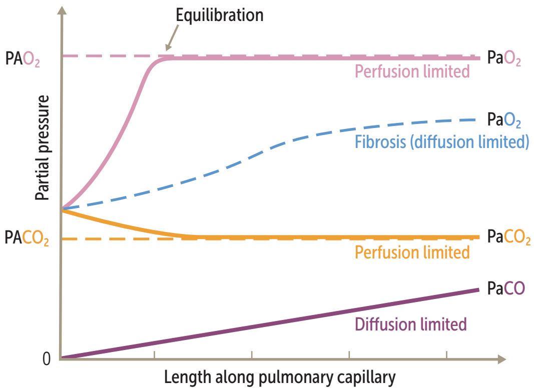
Chronic hypoxic vasoconstriction may lead to pulmonary hypertension +/– cor pulmonale.

Diffusion: $\dot{V}_{gas} = A \times D_k \times \dfrac{P_1 - P_2}{\Delta_x}$ where

A = area, $\Delta_x$ = alveolar wall thickness, $D_k$ = diffusion coefficient of gas, $P_1 - P_2$ = difference in partial pressures.

- A ↓ in emphysema.
- $\Delta_x$ ↑ in pulmonary fibrosis.

DLCO is the extent to which CO passes from air sacs of lungs into blood.




Pa = partial pressure of gas in pulmonary capillary blood
PA = partial pressure of gas in alveolar air

### Pulmonary vascular resistance

$$PVR = \frac{P_{pulm\ artery} - P_{L\ atrium}}{Q}$$

Remember: $\Delta P = Q \times R$, so $R = \Delta P / Q$

$$R = \frac{8\eta l}{\pi r^4}$$

$P_{pulm\ artery}$ = pressure in pulmonary artery
$P_{L\ atrium}$ ≈ pulmonary artery occlusion pressure (also called pulmonary capillary wedge pressure)
Q = cardiac output (flow)
R = resistance
η = viscosity of blood
l = vessel length
r = vessel radius

### Alveolar gas equation

$$P_{AO_2} = P_{IO_2} - \frac{Pa_{CO_2}}{R}$$

$$\approx 150 \text{ mm Hg}^a - \frac{Pa_{CO_2}}{0.8}$$

[a]At sea level breathing room air

$P_{AO_2}$ = alveolar $P_{O_2}$ (mm Hg)
$P_{IO_2}$ = $P_{O_2}$ in inspired air (mm Hg)
$Pa_{CO_2}$ = arterial $P_{CO_2}$ (mm Hg)
R = respiratory quotient = $CO_2$ produced/$O_2$ consumed
A-a gradient = $P_{AO_2} - Pa_{O_2}$. Normal A-a gradient estimated as (age/4) + 4 (eg, for a person <40 years old, gradient should be <14).

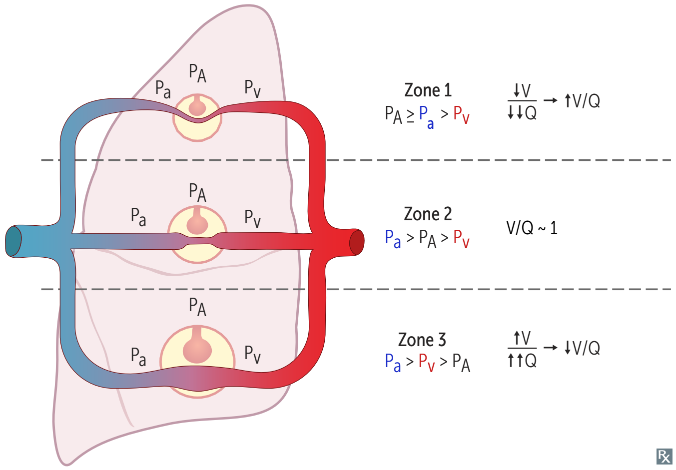
## Oxygen deprivation

| Hypoxia (↓ $O_2$ delivery to tissue) | Hypoxemia (↓ $Pao_2$) | Ischemia (loss of blood flow) |
|---|---|---|
| ↓ cardiac output<br>Hypoxemia<br>Ischemia<br>Anemia<br>CO/cyanide poisoning | Normal A-a gradient<br>▪ High altitude (↓ barometric pressure)<br>▪ Hypoventilation (eg, opioid use, obesity hypoventilation syndrome)<br>↑ A-a gradient<br>▪ $\dot{V}/\dot{Q}$ mismatch<br>▪ Diffusion limitation (eg, fibrosis)<br>▪ Right-to-left shunt | Impeded arterial flow<br>↓ venous drainage |

## Ventilation/perfusion mismatch

Ideally, ventilation is matched to perfusion (ie, $\dot{V}/\dot{Q} = 1$) for adequate gas exchange.
Lung zones:
- $\dot{V}/\dot{Q}$ at apex of lung = 3 (wasted ventilation)
- $\dot{V}/\dot{Q}$ at base of lung = 0.6 (wasted perfusion)

Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.
With exercise (↑ cardiac output), there is vasodilation of apical capillaries → $\dot{V}/\dot{Q}$ ratio approaches 1.
Certain organisms that thrive in high $O_2$ (eg, TB) flourish in the apex.
$\dot{V}/\dot{Q} = 0$ = "oirway" obstruction (shunt). In shunt, 100% $O_2$ does not improve $Pao_2$ (eg, foreign body aspiration).
$\dot{V}/\dot{Q} = \infty$ = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% $O_2$ improves $Pao_2$ (eg, pulmonary embolus).



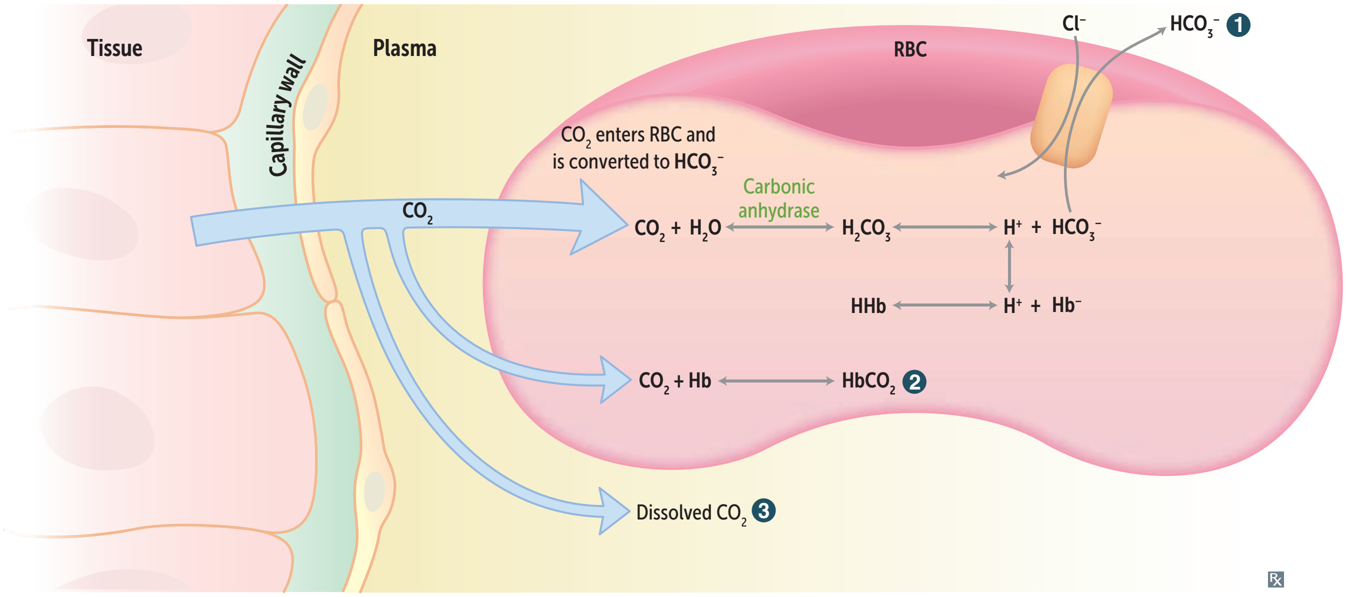
**Carbon dioxide transport**

$CO_2$ is transported from tissues to lungs in 3 forms:

1. $HCO_3^-$ (70%). $HCO_3^-/Cl^-$ transporter on RBC membrane allows $HCO_3^-$ to diffuse out to plasma and $Cl^-$ to diffuse into RBC (chloride shift).
2. Carbaminohemoglobin or $HbCO_2$ (21–25%). $CO_2$ bound to Hb at N-terminus of globin (not heme). $CO_2$ favors deoxygenated form ($O_2$ unloaded).
3. Dissolved $CO_2$ (5–9%).

In lungs, oxygenation of Hb promotes dissociation of $H^+$ from Hb. This shifts equilibrium toward $CO_2$ formation; therefore, $CO_2$ is released from RBCs (Haldane effect).

Majority of blood $CO_2$ is carried as $HCO_3^-$ in the plasma.

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**Response to high altitude**

↓ atmospheric oxygen ($PiO_2$) → ↓ $Pao_2$ → ↑ ventilation → ↓ $Paco_2$ → respiratory alkalosis → altitude sickness (headaches, nausea, fatigue, lightheadedness, sleep disturbance).

Chronic ↑ in ventilation.

↑ erythropoietin → ↑ Hct and Hb (due to chronic hypoxia).

↑ 2,3-BPG (binds to Hb → rightward shift of ODC dissociation curve → ↑ $O_2$ release).

Cellular changes (↑ mitochondria).

↑ renal excretion of $HCO_3^-$ to compensate for respiratory alkalosis (can augment with acetazolamide).

Chronic hypoxic pulmonary vasoconstriction → ↑ pulmonary vascular resistance → pulmonary hypertension, RVH.

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**Response to exercise**

↑ $CO_2$ production.

↑ $O_2$ consumption.

Right shift of ODC.

↑ ventilation to meet $O_2$ demand and remove excess $CO_2$.

$\dot{V}/\dot{Q}$ ratio from apex to base becomes more uniform.

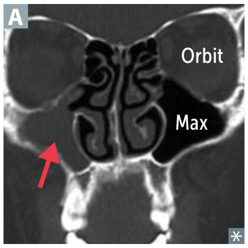
↑ pulmonary blood flow due to ↑ cardiac output.

↓ pH during strenuous exercise (2° to lactic acidosis).

No change in $Pao_2$ and $Paco_2$, but ↑ in venous $CO_2$ content and ↓ in venous $O_2$ content.

## ▸ RESPIRATORY—PATHOLOGY

### Rhinosinusitis




Obstruction of sinus drainage into nasal cavity → inflammation and pain over affected area. Typically affects maxillary sinuses, which drain against gravity due to ostia located superomedially (red arrow points to fluid-filled right maxillary sinus in A).

Superior meatus—drains sphenoid, posterior ethmoid; middle meatus—drains frontal, maxillary, and anterior ethmoid; inferior meatus—drains nasolacrimal duct.

Acute rhinosinusitis is most commonly caused by viruses (eg, rhinovirus); may lead to superimposed bacterial infection, most commonly *H influenzae*, *S pneumoniae*, *M catarrhalis*.

Paranasal sinus infections may extend to the orbits, cavernous sinus, and brain, causing complications (eg, orbital cellulitis, cavernous sinus syndrome, meningitis).

### Epistaxis

Nose bleed. Most commonly occurs in anterior segment of nostril (**Kiesselbach plexus**). Life-threatening hemorrhages occur in posterior segment (sphenopalatine artery, a branch of maxillary artery). Common causes include foreign body, trauma, allergic rhinitis, and nasal angiofibromas (common in adolescent males).

**Kiesselbach** drives his **Lexus** with his **LEGS**: superior **L**abial artery, anterior and posterior **E**thmoidal arteries, **G**reater palatine artery, **S**phenopalatine artery.

### Head and neck cancer

Mostly squamous cell carcinoma. Risk factors include tobacco, alcohol, HPV-16 (oropharyngeal), EBV (nasopharyngeal). Field cancerization: carcinogen damages wide mucosal area → multiple tumors that develop independently after exposure.

Nasopharyngeal carcinoma may present with unilateral nasal obstruction, discharge, epistaxis. Eustachian tube obstruction may lead to otitis media +/– effusion, hearing loss.

### Deep venous thrombosis


Blood clot within a deep vein → swelling, redness A, warmth, pain. Predisposed by Virchow triad (**SHE**):
- **S**tasis (eg, post-op, long drive/flight)
- **H**ypercoagulability (eg, defect in coagulation cascade proteins, such as factor V Leiden; oral contraceptive use; pregnancy)
- **E**ndothelial damage (exposed collagen triggers clotting cascade)

Most pulmonary emboli arise from proximal deep veins of lower extremity (iliac, femoral, popliteal veins).

D-dimer test may be used clinically to rule out DVT if disease probability is low or moderate (high sensitivity, low specificity).

Imaging test of choice is compression ultrasound with Doppler.

Use unfractionated heparin or low-molecular weight heparins (eg, enoxaparin) for prophylaxis and acute management.

Use direct anticoagulants (eg, rivaroxaban, apixaban) for treatment and long-term prevention.

**Pulmonary emboli**

Obstruction of the pulmonary artery or its branches by foreign material (usually thrombus) that originated elsewhere. Affected alveoli are ventilated but not perfused ($\dot{V}/\dot{Q}$ mismatch). May present with sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia, hypoxemia, respiratory alkalosis. Large emboli or saddle embolus A may cause sudden death due to electromechanical dissociation (pulseless electrical activity). CT pulmonary angiography is imaging test of choice for PE (look for filling defects) B. ECG may show sinus tachycardia or, less commonly, S1Q3T3 abnormality.

Lines of Zahn C are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in thrombi formed before death; help distinguish pre- and postmortem thrombi.

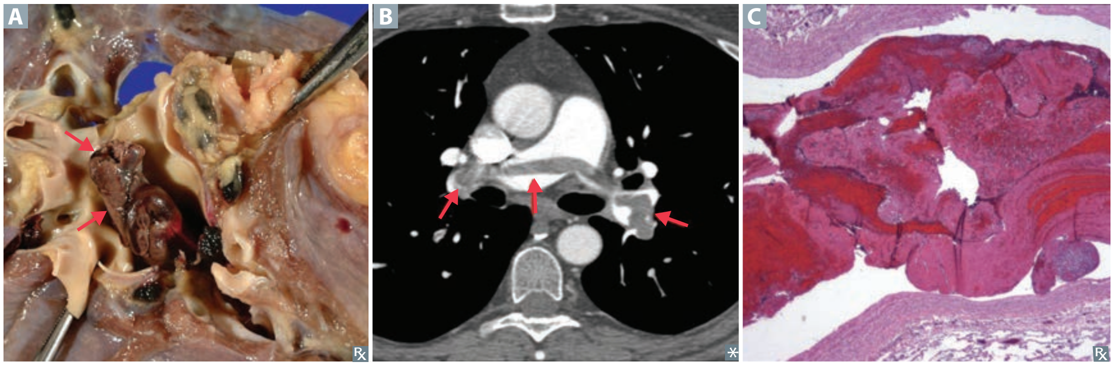
Treatment: anticoagulation (eg, heparin, direct thrombin/factor Xa inhibitors), IVC filter (if anticoagulation is contraindicated).

Types: **F**at, **A**ir, **T**hrombus, **B**acteria, **A**mniotic fluid, **T**umor. An embolus moves like a **FAT BAT**.

Fat emboli—associated with long bone fractures and liposuction; classic triad of hypoxemia, neurologic abnormalities, petechial rash.

Air emboli—nitrogen bubbles precipitate in ascending divers (caisson disease/decompression sickness); treat with hyperbaric $O_2$; or, can be iatrogenic 2° to invasive procedures (eg, central line placement).

Amniotic fluid emboli—typically occurs during labor or postpartum, but can be due to uterine trauma. Can lead to DIC. Rare, but high mortality.

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**Mediastinal pathology**

Normal mediastinum contains heart, thymus, lymph nodes, esophagus, and aorta.

**Mediastinal masses**

Some pathologies (eg, lymphoma, lung cancer, abscess) can occur in any compartment, but there are common associations:

- Anterior—**4 T**'s: **t**hyroid (substernal goiter), **t**hymic neoplasm, **t**eratoma, "**t**errible" lymphoma.
- Middle—esophageal carcinoma, metastases, hiatal hernia, bronchogenic cysts.
- Posterior—neurogenic tumor (eg, neurofibroma), multiple myeloma.

**Mediastinitis**

Inflammation of mediastinal tissues. Commonly due to postoperative complications of cardiothoracic procedures (≤ 14 days), esophageal perforation, or contiguous spread of odontogenic/retropharyngeal infection.

Chronic mediastinitis—also known as fibrosing mediastinitis; due to ↑ proliferation of connective tissue in mediastinum. *Histoplasma capsulatum* is common cause.

Clinical features: fever, tachycardia, leukocytosis, chest pain, and sternal wound drainage.

**Pneumomediastinum**

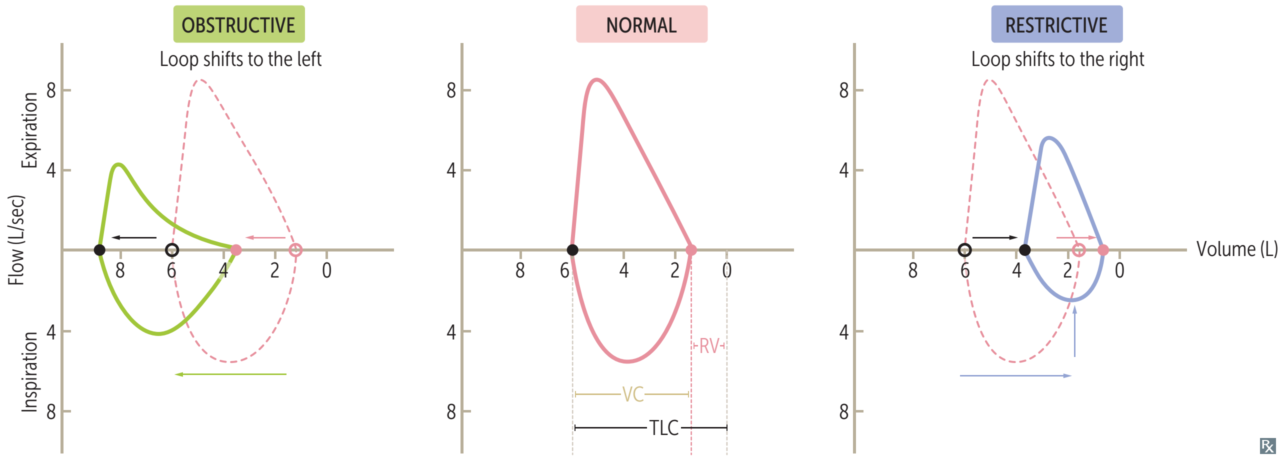
Presence of gas (usually air) in the mediastinum. Can either be spontaneous (due to rupture of pulmonary bleb) or 2° (eg, trauma, iatrogenic, Boerhaave syndrome).

Ruptured alveoli allow tracking of air into the mediastinum via peribronchial and perivascular sheaths.

Clinical features: chest pain, dyspnea, voice change, subcutaneous emphysema, ⊕ Hamman sign (crepitus on cardiac auscultation).

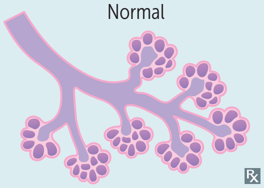
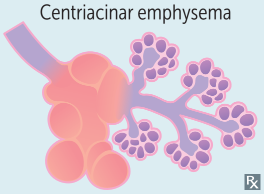
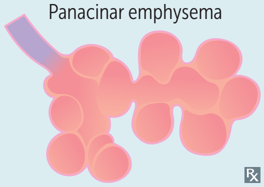
## Flow-volume loops

| FLOW-VOLUME PARAMETER | Obstructive lung disease | Restrictive lung disease |
|---|---|---|
| RV | ↑ | ↓ |
| FRC | ↑ | ↓ |
| TLC | ↑ | ↓ |
| $FEV_1$ | ↓↓ | ↓ |
| FVC | ↓ | ↓ |
| $FEV_1$/FVC | ↓<br>$FEV_1$ decreased more than FVC | Normal or ↑<br>$FEV_1$ decreased proportionately to FVC |



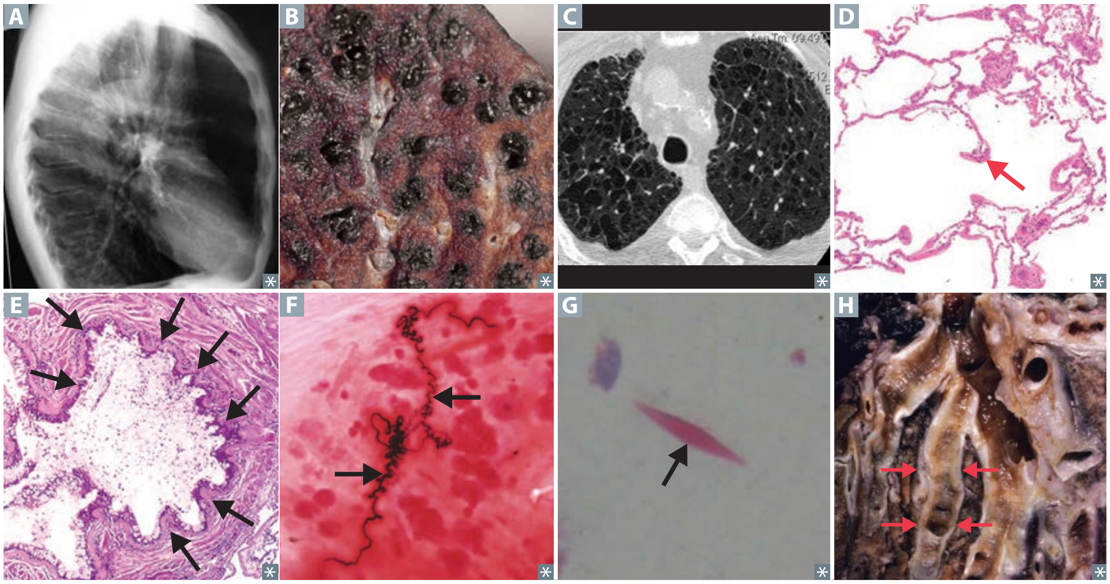
**Obstructive lung diseases**

Obstruction of air flow (↑ FRC, ↑ RV, ↑ TLC) → air trapping in lungs with premature airway closure at high lung volumes (↓↓ $FEV_1$, ↓ FVC ↓ $FEV_1$/FVC ratio). Leads to $\dot{V}/\dot{Q}$ mismatch.

| TYPE | PRESENTATION | PATHOLOGY | OTHER |
|---|---|---|---|
| **Chronic bronchitis** | Wheezing, crackles, cyanosis (hypoxemia due to shunting), dyspnea, $CO_2$ retention, 2° polycythemia. | Hypertrophy and hyperplasia of mucus-secreting glands in bronchi → Reid index (thickness of mucosal gland layer to thickness of wall between epithelium and cartilage) > 50%. DLCO may be normal. | Diagnostic criteria: productive cough for ≥ 3 months in a year for > 2 consecutive years. |
| **Emphysema**<br>Normal<br><br>Centriacinar emphysema<br><br>Panacinar emphysema<br> | Barrel-shaped chest A, expiration is prolonged and/or through pursed lips (increases airway pressure and prevents airway collapse). | Centriacinar—affects respiratory bronchioles while sparing distal alveoli, associated with tobacco **smoking** B C. Frequently in **up**per lobes (**smoke** rises **up**).<br>Panacinar—affects respiratory bronchioles and alveoli, associated with $\alpha_1$-antitrypsin deficiency. Frequently in lower lobes.<br>Enlargement of air spaces ↓ recoil, ↑ compliance, ↓ DLCO from destruction of alveolar walls (arrow in D) and ↓ blood volume in pulmonary capillaries.<br>Imbalance of proteases and antiproteases → ↑ elastase activity → ↑ loss of elastic fibers → ↑ lung compliance. | CXR: ↑ AP diameter, flattened diaphragm, ↑ lung field lucency. Chronic inflammation is mediated by $CD8^+$ T cells, neutrophils, and macrophages. |
| **Asthma** | Asymptomatic baseline with intermittent episodes of coughing, wheezing, tachypnea, dyspnea, hypoxemia, ↓ inspiratory/expiratory ratio, mucus plugging E. Severe attacks may lead to pulsus paradoxus.<br>Triggers: viral URIs, allergens, stress. | Hyperresponsive bronchi → reversible bronchoconstriction. Smooth muscle hypertrophy and hyperplasia, Curschmann spirals F (shed epithelium forms whorled mucous plugs), and Charcot-Leyden crystals G (eosinophilic, hexagonal, double-pointed crystals formed from breakdown of eosinophils in sputum). DLCO normal or ↑. | Type I hypersensitivity reaction.<br>Diagnosis supported by spirometry +/– methacholine challenge.<br>NSAID-exacerbated respiratory disease is a combination of COX inhibition (leukotriene overproduction → airway constriction), chronic sinusitis with nasal polyps, and asthma symptoms. |

**Obstructive lung diseases *(continued)***

| TYPE | PRESENTATION | PATHOLOGY | OTHER |
|---|---|---|---|
| **Bronchiectasis** | Daily purulent sputum, recurrent infections (most often *P aeruginosa*), hemoptysis, digital clubbing. | Chronic necrotizing infection of bronchi or obstruction → permanently dilated airways. | Associated with bronchial obstruction, poor ciliary motility (eg, tobacco smoking, Kartagener syndrome), cystic fibrosis (arrows in H show dilated airway with mucus plug), allergic bronchopulmonary aspergillosis. |




**Restrictive lung diseases**

May lead to ↓ lung volumes (↓ FVC and TLC). PFTs: normal or ↑ $FEV_1$/FVC ratio. Patient presents with short, shallow breaths.

Types:

- Altered respiratory mechanics (extrapulmonary, normal $D_{LCO}$, normal A-a gradient):
  - Respiratory muscle weakness—polio, myasthenia gravis, Guillain-Barré syndrome, ALS
  - Chest wall abnormalities—scoliosis, severe obesity
- Diffuse parenchymal lung diseases, also known as interstitial lung diseases (pulmonary, ↓ $D_{LCO}$, ↑ A-a gradient):
  - Pneumoconioses (eg, coal workers' pneumoconiosis, silicosis, asbestosis)
  - Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granulomas; ↑ ACE and $Ca^{2+}$
  - Idiopathic pulmonary fibrosis
  - Granulomatosis with polyangiitis
  - Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
  - Hypersensitivity pneumonitis
  - Drug toxicity (eg, bleomycin, busulfan, amiodarone, methotrexate)
  - Acute respiratory distress syndrome
  - **Radiation-induced lung injury**—Associated with proinflammatory cytokine release (eg, TNF-α, IL-1, IL-6). May be asymptomatic but most common symptoms are dry cough and dyspnea ± low-grade fever. Acute radiation pneumonitis develops within 3–12 weeks (exudative phase); radiation fibrosis may develop after 6–12 months.

**Idiopathic pulmonary fibrosis**

Progressive fibrotic lung disease of unknown etiology. May involve multiple cycles of lung injury, inflammation, and fibrosis. Associated with cigarette smoking, environmental pollutants, genetic defects.

Findings: progressive dyspnea, fatigue, nonproductive cough, crackles, clubbing. Imaging shows peripheral reticular opacities with traction bronchiectasis +/– "honeycomb" appearance of lung (advanced disease). Histologic pattern: usual interstitial pneumonia.

Complications: pulmonary hypertension, respiratory failure, lung cancer, arrhythmias.

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**Hypersensitivity pneumonitis**

Mixed type III/IV hypersensitivity reaction to environmental antigens. Often seen in farmers and bird-fanciers. Acutely, causes dyspnea, cough, chest tightness, fever, headache. Often self-limiting if stimulus is removed. Chronically, leads to irreversible fibrosis with noncaseating granuloma, alveolar septal thickening, traction bronchiectasis.

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**Sarcoidosis**

Characterized by immune-mediated, widespread noncaseating granulomas A, elevated serum ACE levels, and elevated CD4/CD8 ratio in bronchoalveolar lavage fluid. More common in Black females. Often asymptomatic except for enlarged lymph nodes. CXR shows bilateral adenopathy and coarse reticular opacities B; CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy C.

Associated with Bell palsy, uveitis, granulomas (noncaseating epithelioid, containing microscopic Schaumann and asteroid bodies), lupus pernio (skin lesions on face resembling lupus), interstitial fibrosis (restrictive lung disease), erythema nodosum, rheumatoid arthritis-like arthropathy, hypercalcemia (due to ↑ 1α-hydroxylase–mediated vitamin D activation in macrophages).

Treatment: steroids (if symptomatic).


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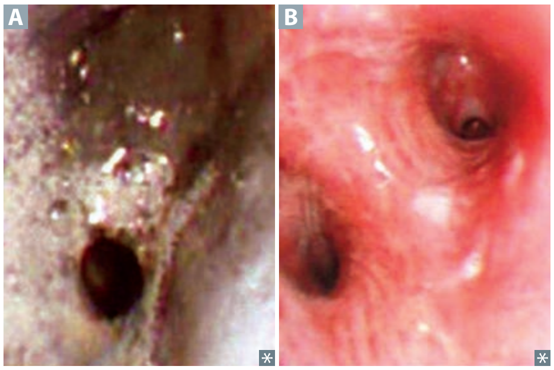
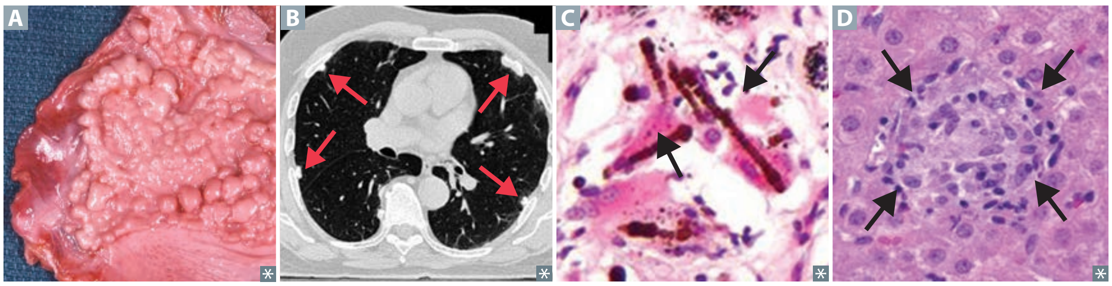
**Inhalation injury and sequelae**

Complication of inhalation of noxious stimuli (eg, smoke). Caused by heat, particulates (< 1 μm diameter), or irritants (eg, $NH_3$) → chemical tracheobronchitis, edema, pneumonia, ARDS. Many patients present 2° to burns, CO inhalation, cyanide poisoning, or arsenic poisoning. Singed nasal hairs or soot in oropharynx common on exam.

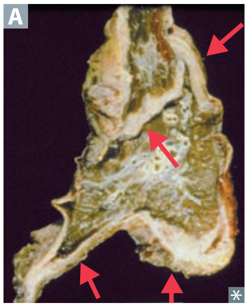
Bronchoscopy shows severe edema, congestion of bronchus, and soot deposition (A, 18 hours after inhalation injury; B, resolution at 11 days after injury).



| | | |
|---|---|---|
| **Pneumoconioses** | Asbestos is from the roof (was common in insulation), but affects the base (lower lobes). Silica, coal, and berries are from the base (earth), but affect the roof (upper lobes). | |
| **Asbestos-related disease** | Asbestos causes asbestosis (pulmonary fibrosis), pleural disease, malignancies. Associated with shipbuilding, roofing, plumbing. "Ivory white," calcified, supradiaphragmatic A and pleural B plaques are pathognomonic.<br>Risk of bronchogenic carcinoma > risk of mesothelioma. ↑ risk of Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules). | Affects lower lobes.<br>Asbestos (ferruginous) bodies are golden-brown fusiform rods resembling dumbbells C, found in alveolar sputum sample, visualized using Prussian blue stain, often obtained by bronchoalveolar lavage.<br>↑ risk of pleural effusions. |
| **Berylliosis** | Associated with exposure to beryllium in aerospace and manufacturing industries. Granulomatous (noncaseating) D on histology and therefore occasionally responsive to steroids. ↑ risk of cancer and cor pulmonale. | Affects upper lobes. |
| **Coal workers' pneumoconiosis** | Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis.<br>Also known as black lung disease. ↑ risk of Caplan syndrome. | Affects upper lobes.<br>Small, rounded nodular opacities seen on imaging.<br>Anthracosis—asymptomatic condition found in many urban dwellers exposed to sooty air. |
| **Silicosis** | Associated with sandblasting, foundries, mines. Macrophages respond to silica and release fibrogenic factors, leading to fibrosis. It is thought that silica may disrupt phagolysosomes and impair macrophages, increasing susceptibility to TB. ↑ risk of cancer, cor pulmonale, and Caplan syndrome. | Affects upper lobes.<br>"Eggshell" calcification of hilar lymph nodes on CXR.<br>The silly egg sandwich I found is mine! |



## Mesothelioma




Malignancy of the pleura associated with asbestosis. May result in hemorrhagic pleural effusion (exudative), pleural thickening A.

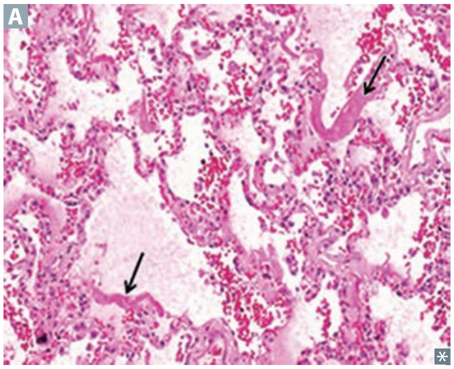
Histology may show psammoma bodies. EM may show polygonal tumor cells with microvili, desmosomes, tonofilaments.

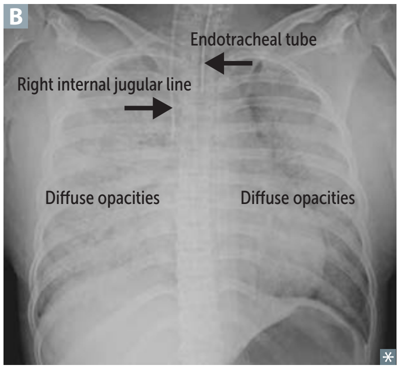
Calretinin and cytokeratin 5/6 ⊕ in almost all mesotheliomas, ⊖ in most carcinomas.

Tobacco smoking is not a risk factor.

## Acute respiratory distress syndrome

| | |
|---|---|
| PATHOPHYSIOLOGY | Alveolar insult → release of pro-inflammatory cytokines → neutrophil recruitment, activation, and release of toxic mediators (eg, reactive oxygen species, proteases, etc) → capillary endothelial damage and ↑ vessel permeability → leakage of protein-rich fluid into alveoli → formation of intra-alveolar hyaline membranes (arrows in A) and noncardiogenic pulmonary edema (normal PCWP).<br>Loss of surfactant also contributes to alveolar collapse. |
| CAUSES | Sepsis (most common), aspiration, pneumonia, trauma, pancreatitis. |
| DIAGNOSIS | Diagnosis of exclusion with the following criteria (**ARDS**):<br>▪ **A**bnormal chest X-ray (bilateral lung opacities) B<br>▪ **R**espiratory failure within 1 week of alveolar insult<br>▪ **D**ecreased $Pa_{O_2}/Fi_{O_2}$ (ratio < 300, hypoxemia due to ↑ intrapulmonary shunting and diffusion abnormalities)<br>▪ **S**ymptoms of respiratory failure are not due to HF/fluid overload |
| CONSEQUENCES | Impaired gas exchange, ↓ lung compliance; pulmonary hypertension. |
| MANAGEMENT | Treat the underlying cause.<br>Mechanical ventilation: ↓ tidal volume, ↑ PEEP (keeps alveoli open during expiration). |



| | |
|---|---|
| **Sleep apnea** | Repeated cessation of breathing > 10 seconds during sleep → disrupted sleep → daytime somnolence. Diagnosis confirmed by sleep study.<br>Nocturnal hypoxia → systemic and pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death.<br>Hypoxia → ↑ EPO release → ↑ erythropoiesis. |
| **Obstructive sleep apnea** | Respiratory effort against airway obstruction. $Pa_{O_2}$ is usually normal during the day. Associated with obesity, loud snoring, daytime sleepiness. Usually caused by excess parapharyngeal/oropharyngeal tissue in adults, adenotonsillar hypertrophy in children. Treatment: weight loss, CPAP, dental devices, hypoglossal nerve stimulation, upper airway surgery. |
| **Central sleep apnea** | Impaired respiratory effort due to CNS injury/toxicity, Congestive HF, opioids. May be associated with Cheyne-Stokes respirations (oscillations between apnea and hyperpnea). Treatment: positive airway pressure. |
| **Obesity hypoventilation syndrome** | Also called Pickwickian syndrome. Obesity (BMI ≥ 30 kg/m$^2$) → hypoventilation → ↑ $Pa_{CO_2}$ during waking hours (retention); ↓ $Pa_{O_2}$ and ↑ $Pa_{CO_2}$ during sleep. Treatment: weight loss, positive airway pressure. |

| | |
|---|---|
| **Pulmonary hypertension** | Elevated mean pulmonary artery pressure (> 20 mm Hg) at rest. Results in arteriosclerosis, medial hypertrophy, intimal fibrosis of pulmonary arteries, plexiform lesions. ↑ pulmonary vascular resistance → ↑ RV pressure → RVH, RV failure. |
| ETIOLOGIES | |
| **Pulmonary arterial hypertension** | Often idiopathic. Females > males. Heritable PAH can be due to an inactivating mutation in *BMPR2* gene (normally inhibits vascular smooth muscle proliferation); poor prognosis. Pulmonary vasculature endothelial dysfunction results in ↑ vasoconstrictors (eg, endothelin) and ↓ vasodilators (eg, NO and prostacyclins).<br>Other causes include drugs (eg, amphetamines, cocaine), connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis. |
| **Left heart disease** | Causes include systolic/diastolic dysfunction and valvular disease. |
| **Lung diseases or hypoxia** | Destruction of lung parenchyma (eg, COPD), lung inflammation/fibrosis (eg, interstitial lung diseases), hypoxemic vasoconstriction (eg, obstructive sleep apnea, living in high altitude). |
| **Chronic thromboembolic** | Recurrent microthrombi → ↓ cross-sectional area of pulmonary vascular bed. |
| **Multifactorial** | Causes include hematologic, systemic, and metabolic disorders, along with compression of the pulmonary vasculature by a tumor. |

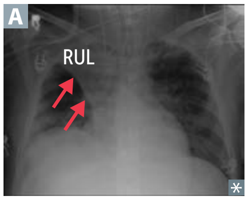
## Physical findings in select lung diseases

| ABNORMALITY | BREATH SOUNDS | PERCUSSION | FREMITUS | TRACHEAL DEVIATION |
|---|---|---|---|---|
| **Pleural effusion** | ↓ | Dull | ↓ | None if small<br>Away from side of lesion if large |
| **Atelectasis** | ↓ | Dull | ↓ | Toward side of lesion |
| **Simple pneumothorax** | ↓ | Hyperresonant | ↓ | None |
| **Tension pneumothorax** | ↓ | Hyperresonant | ↓ | Away from side of lesion |
| **Consolidation (lobar pneumonia, pulmonary edema)** | Bronchial breath sounds; late inspiratory crackles, egophony, whispered pectoriloquy | Dull | ↑ | None |

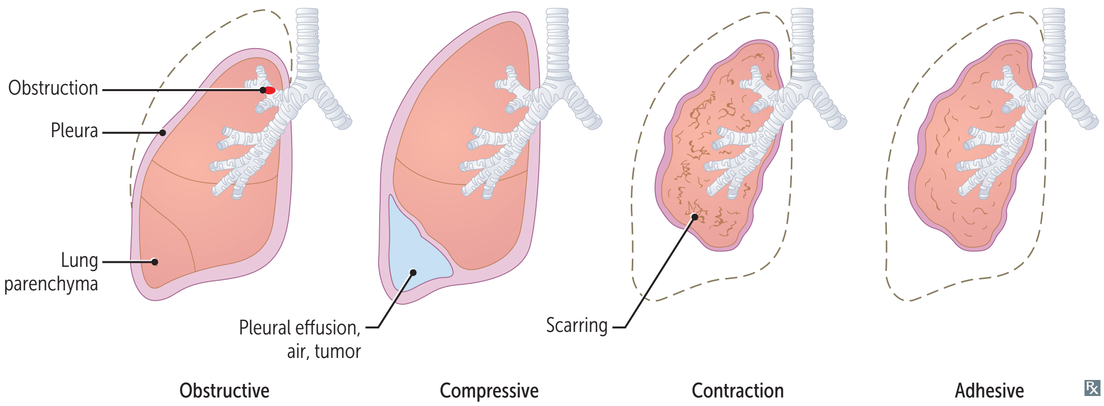
### Digital clubbing


Increased angle between nail bed and nail plate (> 180°) A. Pathophysiology not well understood; in patients with intrapulmonary shunt, platelets and megakaryocytes become lodged in digital vasculature → local release of PDGF and VEGF. Can be hereditary or acquired. Causes include respiratory diseases (eg, idiopathic pulmonary fibrosis, cystic fibrosis, bronchiectasis, lung cancer), cardiovascular diseases (eg, cyanotic congenital heart disease), infections (eg, lung abscess, TB), and others (eg, IBD). Not typically associated with COPD or asthma.

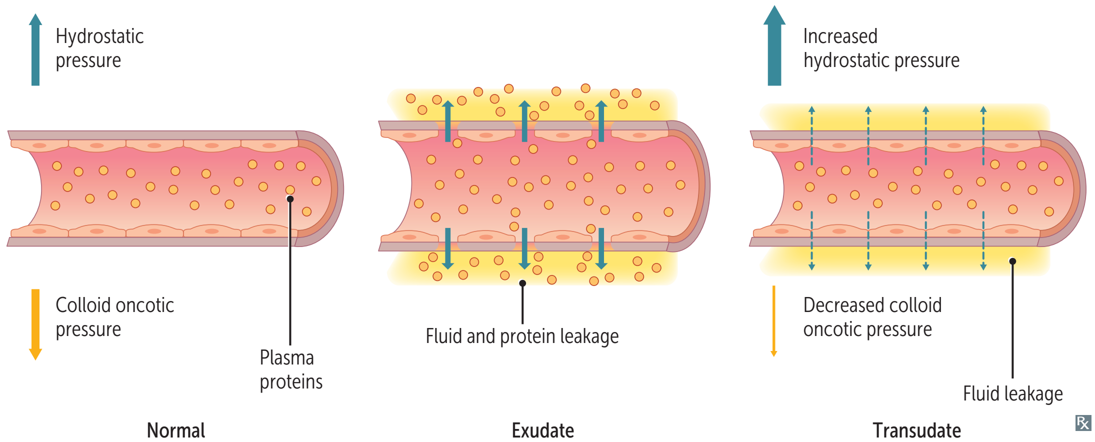
### Atelectasis

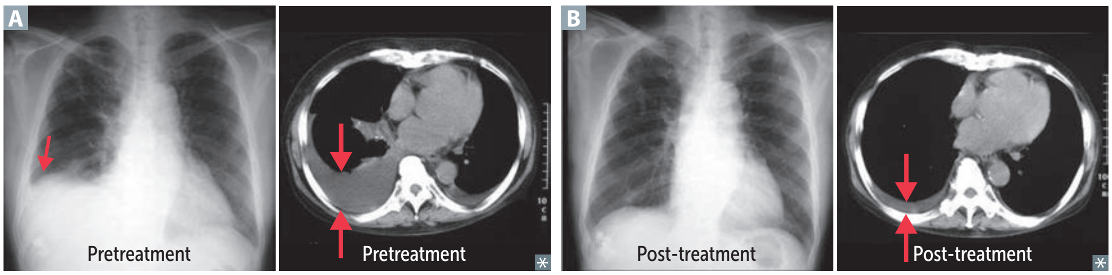



Alveolar collapse (right upper lobe collapse against mediastinum in A). Multiple causes:
- Obstructive—airway obstruction prevents new air from reaching distal airways, old air is resorbed (eg, foreign body, mucous plug, tumor)
- Compressive—external compression on lung decreases lung volumes (eg, space-occupying lesion, pleural effusion)
- Contraction (cicatrization)—scarring of lung parenchyma that distorts alveoli (eg, sarcoidosis)
- Adhesive—due to lack of surfactant (eg, NRDS in premature babies)

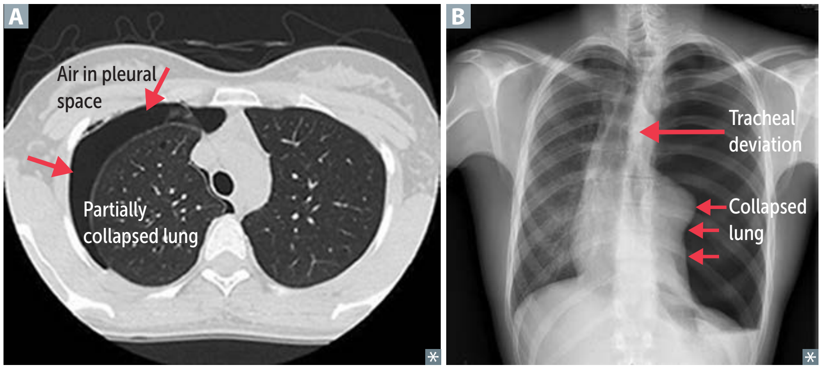


| | |
|---|---|
| **Pleural effusions** | Excess accumulation of fluid A between pleural layers → restricted lung expansion during inspiration. Can be treated with thoracentesis to remove/reduce fluid B. Based on the Light criteria, fluid is exudate if pleural fluid protein/serum protein > 0.5, pleural fluid LDH/serum LDH > 0.6, or pleural fluid LDH > 2/3 upper limit of normal serum LDH. |
| **Exudate** | Cloudy fluid (cellular). Due to malignancy, inflammation/infection (eg, pneumonia, collagen vascular disease), trauma (occurs in states of ↑ vascular permeability). Often needs to be drained due to risk of infection. |
| **Transudate** | Clear fluid (hypocellular). Due to ↑ hydrostatic pressure (eg, HF, $Na^+$ retention) and/or ↓ oncotic pressure (eg, nephrotic syndrome, cirrhosis). |
| **Lymphatic** | Also known as chylothorax. Due to thoracic duct injury from trauma or malignancy. Milky-appearing fluid; ↑ triglycerides. |



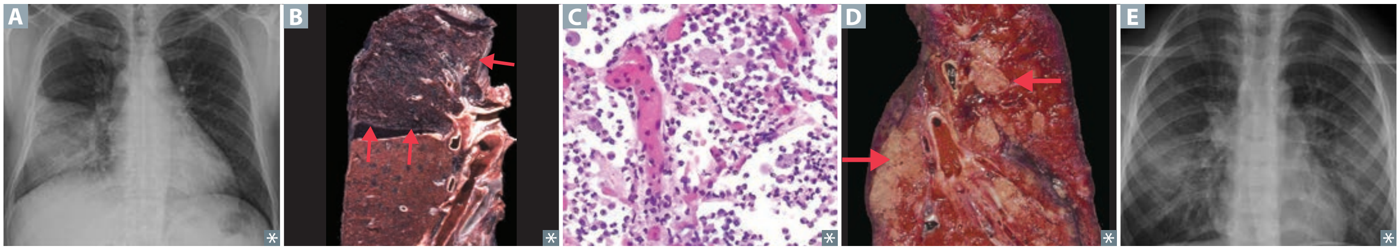



| | |
|---|---|
| **Pneumothorax** | Accumulation of air in pleural space A. Dyspnea, uneven chest expansion. Chest pain, ↓ tactile fremitus, hyperresonance, and diminished breath sounds, all on the affected side. |
| **Primary spontaneous pneumothorax** | Due to rupture of apical subpleural bleb or cysts. Occurs most frequently in tall, thin, young males. Associated with tobacco smoking. |
| **Secondary spontaneous pneumothorax** | Due to diseased lung (eg, bullae in emphysema, Marfan syndrome, infections), mechanical ventilation with use of high pressures → barotrauma. |
| **Traumatic pneumothorax** | Caused by blunt (eg, rib fracture), penetrating (eg, gunshot), or iatrogenic (eg, central line placement, lung biopsy, barotrauma due to mechanical ventilation) trauma. |
| **Tension pneumothorax** | Can be from any of the above. Air enters pleural space but cannot exit. Increasing trapped air → tension pneumothorax. Trachea deviates away from affected lung B. May lead to increased intrathoracic pressure → mediastinal displacement → kinking of IVC → ↓ venous return → ↓ cardiac output, obstructive shock (hypotension, tachycardia), jugular venous distention. Needs immediate needle decompression and chest tube placement. |



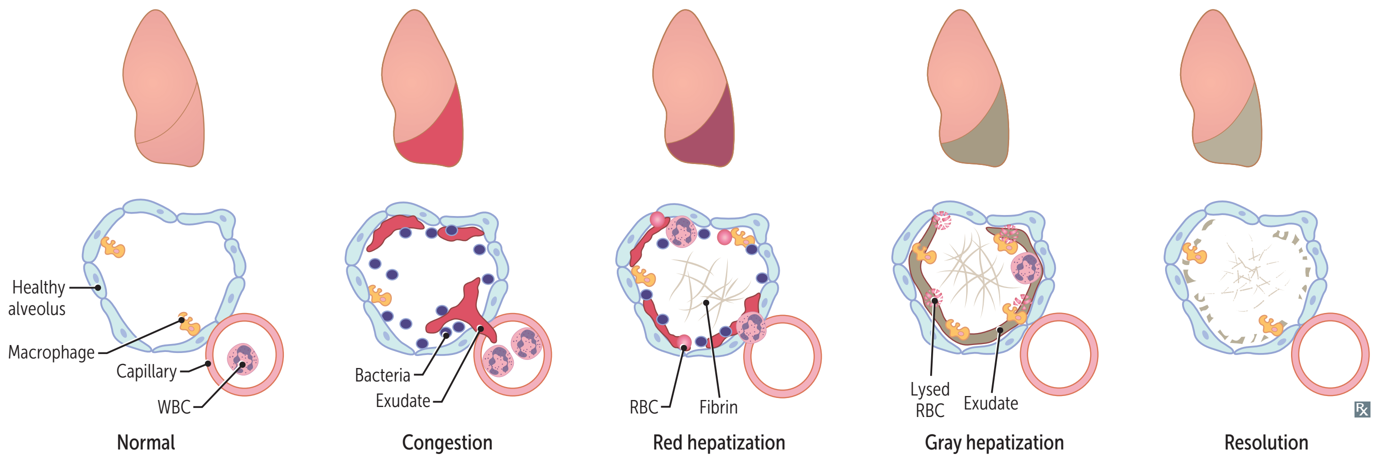
## Pneumonia

| TYPE | TYPICAL ORGANISMS | CHARACTERISTICS |
|---|---|---|
| **Lobar pneumonia** | *S pneumoniae* (most common), *Legionella*, *Klebsiella* | Intra-alveolar exudate → consolidation A; may involve entire lobe B or the whole lung. |
| **Bronchopneumonia** | *S pneumoniae*, *S aureus*, *H influenzae*, *Klebsiella* | Acute inflammatory infiltrates C from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobe D. |
| **Interstitial (atypical) pneumonia** | *Mycoplasma*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, *Legionella*, *Coxiella burnetii*, viruses (RSV, CMV, influenza, adenovirus) | Diffuse patchy inflammation localized to interstitial areas at alveolar walls; CXR shows bilateral multifocal opacities E. Generally follows a more indolent course ("walking" pneumonia). |
| **Cryptogenic organizing pneumonia** | Etiology unknown. ⊖ sputum and blood cultures, often responds to steroids but not to antibiotics. | Formerly known as bronchiolitis obliterans organizing pneumonia (BOOP). Noninfectious pneumonia characterized by inflammation of bronchioles and surrounding structure. |

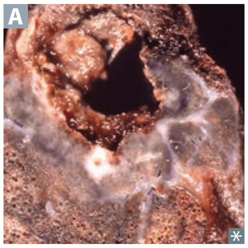


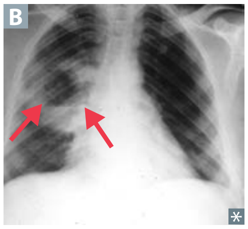

## Natural history of lobar pneumonia

| | Congestion | Red hepatization | Gray hepatization | Resolution |
|---|---|---|---|---|
| DAYS | 1–2 | 3–4 | 5–7 | 8+ |
| FINDINGS | Red-purple, partial consolidation of parenchyma<br>Exudate with mostly bacteria | Red-brown consolidation<br>Exudate with fibrin, bacteria, RBCs, WBCs<br>Reversible | Uniformly gray<br>Exudate full of WBCs, lysed RBCs, and fibrin | Enzymatic digestion of exudate by macrophages |



## Lung abscess





Localized collection of pus within parenchyma A. Caused by aspiration of oropharyngeal contents (especially in patients predisposed to loss of consciousness [eg, alcohol overuse, epilepsy]) or bronchial obstruction (eg, cancer).

Air-fluid levels B often seen on CXR; presence suggests cavitation. Due to anaerobes (eg, *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*) or *S aureus*.

Treatment: antibiotics, drainage, or surgery.

Lung abscess 2° to aspiration is most often found in right lung. Location depends on patient's position during aspiration: RLL if upright, RUL or RML if recumbent.

## Lung cancer

Leading cause of cancer death.

Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic "coin" lesion on CXR or noncalcified nodule on CT.

Sites of metastases from lung cancer: liver (jaundice, hepatomegaly), adrenals, bone (pathologic fracture), brain; "Lung 'mets' Love affective boneheads and brainiacs."

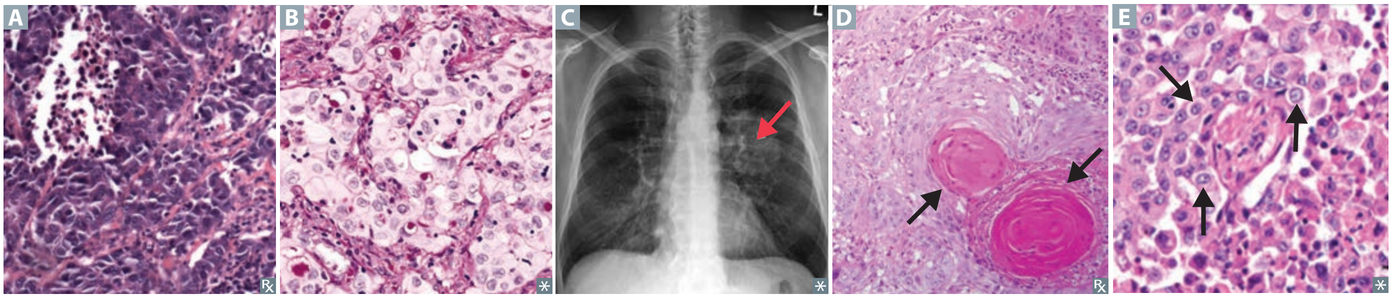
In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon, prostate, and bladder cancer.

SPHERE of complications: Superior vena cava/thoracic outlet syndromes, Pancoast tumor, Horner syndrome, Endocrine (paraneoplastic), Recurrent laryngeal nerve compression (hoarseness), Effusions (pleural or pericardial).

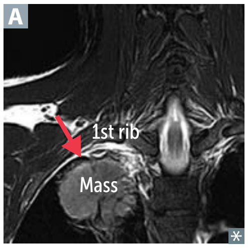
Risk factors include tobacco smoking, secondhand smoke, radiation, environmental exposures (eg, radon, asbestos), pulmonary fibrosis, family history.

Squamous and small cell carcinomas are sentral (central) and often caused by smoking.

| TYPE | LOCATION | CHARACTERISTICS | HISTOLOGY |
|---|---|---|---|
| **Small cell** | | | |
| **Small cell (oat cell) carcinoma** | Central | Undifferentiated → very aggressive. May produce ACTH (Cushing syndrome), ADH (SIADH), or Antibodies against presynaptic $Ca^{2+}$ channels (Lambert-Eaton myasthenic syndrome) or neurons (paraneoplastic myelitis, encephalitis, subacute cerebellar degeneration). Amplification of *myc* oncogenes common. Managed with chemotherapy +/– radiation. | Neoplasm of neuroendocrine Kulchitsky cells → small dark blue cells A. Chromogranin A ⊕, neuron-specific enolase ⊕, synaptophysin ⊕. |
| **Non-small cell** | | | |
| **Adenocarcinoma** | Peripheral | Most common 1° lung cancer. Most common subtype in people who do not smoke. More common in females than males. Activating mutations include *KRAS*, *EGFR*, and *ALK*. Associated with hypertrophic osteoarthropathy (clubbing). Bronchioloalveolar subtype (adenocarcinoma in situ): CXR often shows hazy infiltrates similar to pneumonia; better prognosis. | Glandular pattern, often stains mucin ⊕ B. Bronchioloalveolar subtype: grows along alveolar septa → apparent "thickening" of alveolar walls. Tall, columnar cells containing mucus. |
| **Squamous cell carcinoma** | Central | Hilar mass C arising from bronchus; cavitation; cigarettes; hypercalcemia (produces PTHrP). | Keratin pearls D and intercellular bridges (desmosomes). |
| **Large cell carcinoma** | Peripheral | Highly anaplastic undifferentiated tumor. Strong association with tobacco smoking. May produce hCG → gynecomastia. Less responsive to chemotherapy; removed surgically. Poor prognosis. | Pleomorphic giant cells E. |
| **Bronchial carcinoid tumor** | Central or peripheral | Excellent prognosis; metastasis rare. Symptoms due to mass effect or carcinoid syndrome (flushing, diarrhea, wheezing). | Nests of neuroendocrine cells; chromogranin A ⊕. |



**Pancoast tumor**




Also known as superior sulcus tumor. Carcinoma that occurs in the apex of lung A may cause Pancoast syndrome by invading/compressing local structures.

Compression of locoregional structures may cause array of findings:

- Recurrent laryngeal nerve → hoarseness
- Stellate ganglion → Horner syndrome (ipsilateral ptosis, miosis, anhidrosis)
- Superior vena cava → SVC syndrome
- Brachiocephalic vein → brachiocephalic syndrome (unilateral symptoms)
- Brachial plexus → shoulder pain, sensorimotor deficits (eg, atrophy of intrinsic muscles of the hand)
- Phrenic nerve → hemidiaphragm paralysis (hemidiaphragm elevation on CXR)

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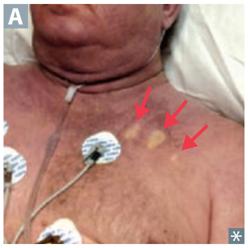
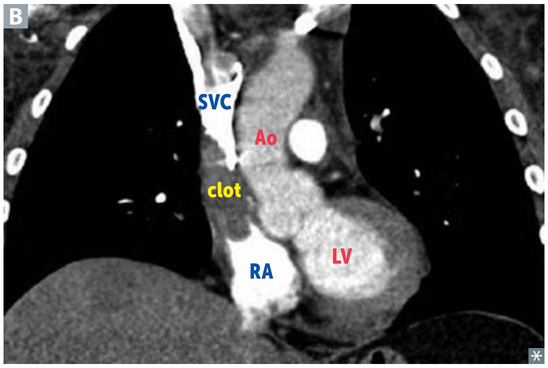
**Superior vena cava syndrome**




An obstruction of the SVC that impairs blood drainage from the head ("facial plethora"; note blanching after fingertip pressure in A), neck (jugular venous distention), and upper extremities (edema). Commonly caused by malignancy (eg, mediastinal mass, Pancoast tumor) and thrombosis from indwelling catheters B. Medical emergency. Can raise intracranial pressure (if obstruction is severe) → headaches, dizziness, ↑ risk of aneurysm/rupture of intracranial arteries.

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## ▸ RESPIRATORY—PHARMACOLOGY

| | | |
|---|---|---|
| **$H_1$-blockers** | Also called antihistamines. Reversible inhibitors of $H_1$ histamine receptors. May function as neutral antagonists or inverse agonists. | |
| **First generation** | Diphenhydramine, dimenhydrinate, chlorpheniramine, doxylamine. | Names usually contain "-en/-ine" or "-en/-ate." |
| CLINICAL USE | Allergy, motion sickness, vomiting in pregnancy, sleep aid. | |
| ADVERSE EFFECTS | Sedation, antimuscarinic, anti-α-adrenergic. | |
| **Second generation** | Loratadine, fexofenadine, desloratadine, cetirizine. | Names usually end in "-adine." Setirizine (cetirizine) is second-generation agent. |
| CLINICAL USE | Allergy. | |
| ADVERSE EFFECTS | Far less sedating than 1st generation because of ↓ entry into CNS. | |

| | |
|---|---|
| **Dextromethorphan** | Antitussive (antagonizes NMDA glutamate receptors). Synthetic codeine analog. Has mild opioid effect when used in excess. Naloxone can be given for overdose. Mild abuse potential. May cause serotonin syndrome if combined with other serotonergic agents. |

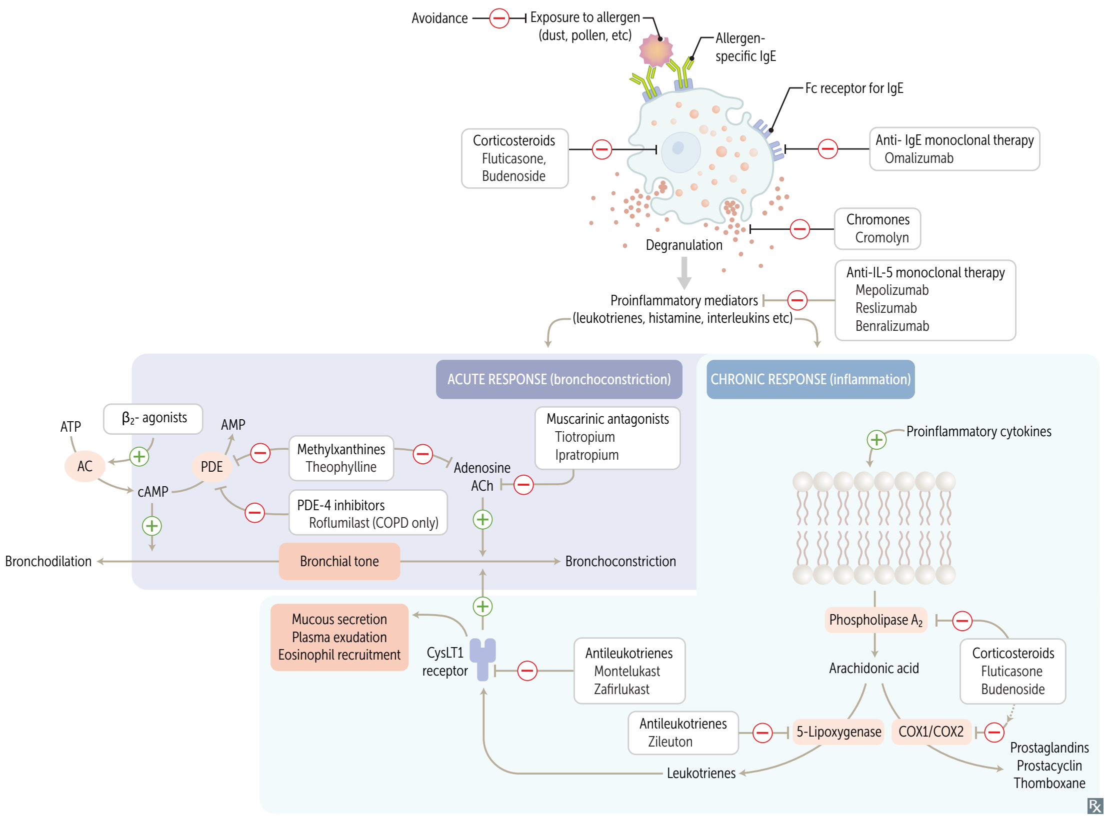
## Pseudoephedrine, phenylephrine

| | |
|---|---|
| MECHANISM | Activation of α-adrenergic receptors in nasal mucosa → local vasoconstriction. |
| CLINICAL USE | Reduce hyperemia, edema (used as nasal decongestants); open obstructed eustachian tubes. |
| ADVERSE EFFECTS | Hypertension. Rebound congestion (rhinitis medicamentosa) if used more than 4–6 days. Associated with tachyphylaxis. Can also cause CNS stimulation/anxiety (pseudoephedrine). |

## Pulmonary hypertension drugs

| DRUG | MECHANISM | CLINICAL NOTES |
|---|---|---|
| **Endothelin receptor antagonists** | Competitively antagonizes endothelin-1 receptors → ↓ pulmonary vascular resistance. | Hepatotoxic (monitor LFTs).<br>Example: bosentan. |
| **PDE-5 inhibitors** | Inhibits PDE-5 → ↑ cGMP → prolonged vasodilatory effect of NO. | Also used to treat erectile dysfunction. Contraindicated when taking nitroglycerin or other nitrates (due to risk of severe hypotension).<br>Example: sildenafil. |
| **Prostacyclin analogs** | $PGI_2$ (prostacyclin) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds. Inhibits platelet aggregation. | Side effects: flushing, jaw pain.<br>Examples: epoprostenol, iloprost. |

| | |
|---|---|
| **Asthma drugs** | Bronchoconstriction is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways. |
| **Inhaled $\beta_2$-agonists** | **Albuterol**—relaxes bronchial smooth muscle (short acting $\beta_2$-agonist). For acute exacerbations. Can cause tremor, arrhythmia.<br>**Salmeterol, formoterol**—long-acting agents for prophylaxis. Can cause tremor, arrhythmia. |
| **Inhaled corticosteroids** | **Fluticasone, budesonide**—inhibit the synthesis of virtually all cytokines. Inactivate NF-κB, the transcription factor that induces production of TNF-α and other inflammatory agents. 1st-line therapy for chronic asthma. Use a spacer or rinse mouth after use to prevent oral thrush. |
| **Muscarinic antagonists** | **Tiotropium, ipratropium**—competitively block muscarinic receptors, preventing bronchoconstriction. Also used for COPD. Tiotropium is long acting. |
| **Antileukotrienes** | **Montelukast, zafirlukast**—block leukotriene receptors (CysLT1). Especially good for aspirin-induced and exercise-induced asthma.<br>**Zileuton**—5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes. Hepatotoxic. |
| **Anti-IgE monoclonal therapy** | **Omalizumab**—binds mostly unbound serum IgE and blocks binding to FcεRI. Used in allergic asthma with ↑ IgE levels resistant to inhaled steroids and long-acting $\beta_2$-agonists. |
| **Methylxanthines** | **Theophylline**—likely causes bronchodilation by inhibiting phosphodiesterase → ↑ cAMP levels due to ↓ cAMP hydrolysis. Limited use due to narrow therapeutic index (cardiotoxicity, neurotoxicity); metabolized by cytochrome P-450. Blocks actions of adenosine. |
| **Chromones** | **Cromolyn**—prevents mast cell degranulation. Prevents acute asthma symptoms. Rarely used. |
| **Anti-IL-5 monoclonal therapy** | Prevents eosinophil differentiation, maturation, activation, and survival mediated by IL-5 stimulation. For maintenance therapy in severe eosinophilic asthma.<br>**Mepolizumab, reslizumab**—against IL-5.<br>**Benralizumab**—against IL-5 receptor α. |



HIGH-YIELD SYSTEMS

# Rapid Review

*"Study without thought is vain: thought without study is dangerous."*

—Confucius

*"It is better, of course, to know useless things than to know nothing."*

—Lucius Annaeus Seneca

*"For every complex problem there is an answer that is clear, simple, and wrong."*

—H. L. Mencken

The following tables represent a collection of high-yield associations between diseases and their clinical findings, treatments, and key associations. They can be quickly reviewed in the days before the exam.

## ▸ CLASSIC PRESENTATIONS

| CLINICAL PRESENTATION | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| Gout, intellectual disability, self-mutilating behavior in a boy | Lesch-Nyhan syndrome (HGPRT deficiency, X-linked recessive) | 37 |
| Situs inversus, chronic ear infections, sinusitis, bronchiectasis, infertility | Kartagener syndrome (dynein arm defect affecting cilia) | 49 |
| Blue sclera | Osteogenesis imperfecta (type I collagen defect) | 51 |
| Elastic skin, hypermobility of joints, ↑ bleeding tendency | Ehlers-Danlos syndrome (type V collagen defect, type III collagen defect seen in vascular subtype of ED) | 51 |
| Arachnodactyly, lens dislocation (upward and temporal), aortic dissection, hyperflexible joints | Marfan syndrome (fibrillin defect) | 52 |
| Arachnodactyly, pectus deformity, lens dislocation (downward) | Homocystinuria (autosomal recessive) | 52 |
| Café-au-lait spots (unilateral), polyostotic fibrous dysplasia, precocious puberty, multiple endocrine abnormalities | McCune-Albright syndrome ($G_s$-protein activating mutation) | 57 |
| Meconium ileus in neonate, recurrent pulmonary infections, nasal polyps, pancreatic insufficiency, infertility/subfertility | Cystic fibrosis (*CFTR* gene defect, chr 7, Phe508 deletion) | 60 |
| Calf pseudohypertrophy | Muscular dystrophy (most commonly Duchenne, due to X-linked recessive frameshift mutation of dystrophin gene) | 61 |
| Child uses arms to stand up from squat | Duchenne muscular dystrophy (Gowers sign) | 61 |
| Slow, progressive muscle weakness in boys | Becker muscular dystrophy (X-linked non-frameshift deletions in dystrophin; less severe than Duchenne) | 61 |
| Infant with cleft lip/palate, microcephaly or holoprosencephaly, polydactyly, cutis aplasia | Patau syndrome (trisomy 13) | 63 |
| Infant with microcephaly, rocker-bottom feet, clenched hands, and structural heart defect | Edwards syndrome (trisomy 18) | 63 |
| Single palmar crease | Down syndrome | 63 |
| Confusion, ophthalmoplegia/nystagmus, ataxia | Wernicke encephalopathy | 66 |
| Dilated cardiomyopathy/high-output heart failure, edema, alcoholism or malnutrition | Wet beriberi (thiamine [vitamin $B_1$] deficiency) | 66 |
| Burning feet syndrome | Vitamin $B_5$ deficiency | 67 |
| Dermatitis, dementia, diarrhea | Pellagra (niacin [vitamin $B_3$] deficiency) | 67 |
| Swollen gums, mucosal bleeding, poor wound healing, petechiae | Scurvy (vitamin C deficiency: can't hydroxylate proline/lysine for collagen synthesis); tea and toast diet | 69 |
| Bowlegs in children, bone pain, and muscle weakness | Rickets (children), osteomalacia (adults); vitamin D deficiency | 70 |
| Hemorrhagic disease of newborn with ↑ PT, ↑ PTT | Vitamin K deficiency | 71 |
| Bluish-black connective tissue, ear cartilage, sclerae; urine turns black on prolonged exposure to air | Alkaptonuria (homogentisate oxidase deficiency; ochronosis) | 84 |
| Chronic exercise intolerance with myalgia, fatigue, painful cramps, myoglobinuria | McArdle disease (skeletal muscle glycogen phosphorylase deficiency) | 87 |

| CLINICAL PRESENTATION | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| Infant with hypoglycemia, hepatomegaly | Cori disease (debranching enzyme deficiency) or Von Gierke disease (glucose-6-phosphatase deficiency, more severe) | 87 |
| Myopathy (infantile hypertrophic cardiomyopathy), exercise intolerance | Pompe disease (lysosomal α-1,4-glucosidase deficiency) | 87 |
| "Cherry-red spots" on macula | Tay-Sachs (ganglioside accumulation) or Niemann-Pick (sphingomyelin accumulation), central retinal artery occlusion | 88, 557 |
| Hepatosplenomegaly, pancytopenia, osteoporosis, avascular necrosis of femoral head, bone crises | Gaucher disease (glucocerebrosidase [β-glucosidase] deficiency) | 88 |
| Achilles tendon xanthoma | Familial hypercholesterolemia (↓ LDL receptor signaling) | 94 |
| Recurrent *Neisseria* infection | Terminal complement deficiencies (C5-C9) | 107 |
| Anaphylaxis following blood transfusion | IgA deficiency | 116 |
| Male child, recurrent infections, no mature B cells | Bruton disease (X-linked agammaglobulinemia) | 116 |
| Recurrent cold (noninflamed) abscesses, eczema, high serum IgE, ↑ eosinophils | Hyper-IgE syndrome (Job syndrome: neutrophil chemotaxis abnormality) | 116 |
| Late separation (>30 days) of umbilical cord, no pus, recurrent skin and mucosal bacterial infections | Leukocyte adhesion deficiency (type 1; defective LFA-1 integrin) | 117 |
| Recurrent infections and granulomas with catalase ⊕ organisms | Chronic granulomatous disease (defect of NAPDH oxidase) | 117 |
| Fever, vomiting, diarrhea, desquamating rash following use of nasal pack or tampon | Staphylococcal toxic shock syndrome | 135 |
| "Strawberry tongue" | Scarlet fever<br>Kawasaki disease | 136, 314 |
| Colon cancer diagnosed a few years after endocarditis | *Streptococcus bovis* | 137 |
| Abdominal pain, diarrhea, leukocytosis, recent antibiotic use | *Clostridium difficile* infection | 138 |
| Flaccid paralysis in newborn after ingestion of honey | *Clostridium botulinum* infection (floppy baby syndrome) | 138 |
| Tonsillar pseudomembrane with "bull's neck" appearance | *Corynebacterium diphtheria* infection | 139 |
| Back pain, fever, night sweats | Pott disease (vertebral TB) | 140 |
| Adrenal insufficiency, fever, DIC | Waterhouse-Friderichsen syndrome (meningococcemia) | 142, 357 |
| Red "currant jelly" sputum in patients with alcohol overuse or diabetes | *Klebsiella pneumoniae* pneumonia | 145 |
| Large rash with bull's-eye appearance | Erythema migrans from *Ixodes* tick bite (Lyme disease: *Borrelia*) | 146 |
| Ulcerated genital lesion | Nonpainful, indurated: chancre (1° syphilis, *Treponema pallidum*)<br>Painful, with exudate: chancroid *(Haemophilus ducreyi)* | 147, 184 |
| Pupil accommodates but doesn't react to light | Neurosyphilis (Argyll Robertson pupil) | 147 |
| Smooth, moist, painless, wart-like white lesions on genitals | Condylomata lata (2° syphilis) | 147 |
| Fever, chills, headache, myalgia following antibiotic treatment for syphilis | Jarisch-Herxheimer reaction (due to host response to sudden release of bacterial antigens) | 148 |

| CLINICAL PRESENTATION | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| Dog or cat bite resulting in infection (cellulitis, osteomyelitis) | *Pasteurella multocida* (cellulitis at inoculation site) | 149 |
| Atypical "walking pneumonia" with x-ray looking worse than the patient | *Mycoplasma pneumoniae* infection | 150 |
| Rash on palms and soles | Coxsackie A, 2° syphilis, Rocky Mountain spotted fever | 150 |
| Black eschar on face of patient with diabetic ketoacidosis and/or neutropenia | *Mucor* or *Rhizopus* fungal infection | 153 |
| Chorioretinitis, hydrocephalus, intracranial calcifications | Congenital toxoplasmosis | 156 |
| Pruritus, serpiginous rash after walking barefoot | Hookworm (*Ancylostoma* spp, *Necator americanus*) | 159 |
| Child with fever later develops red rash on face that spreads to body | Erythema infectiosum/fifth disease (“slapped cheeks” appearance, caused by parvovirus B19) | 164 |
| Fever, cough, conjunctivitis, coryza, diffuse rash | Measles | 170 |
| Small, irregular red spots on buccal/lingual mucosa with blue-white centers | Koplik spots (measles [rubeola] virus) | 170 |
| Bounding pulses, wide pulse pressure, diastolic heart murmur, head bobbing | Aortic regurgitation | 300 |
| Systolic ejection murmur (crescendo-decrescendo), narrow pulse pressure, pulsus parvus et tardus | Aortic stenosis | 300 |
| Continuous “machine-like” heart murmur | PDA (close with indomethacin; keep open with PGE analogs) | 300 |
| Chest pain on exertion | Angina (stable: with moderate exertion; unstable: with minimal exertion or at rest) | 312 |
| Chest pain with ST depressions on ECG | Angina (⊖ troponins) or NSTEMI (⊕ troponins) | 312 |
| Chest pain, pericardial effusion/friction rub, persistent fever following MI | Dressler syndrome (autoimmune-mediated post-MI fibrinous pericarditis, 2 weeks to several months after acute episode) | 317 |
| Distant heart sounds, distended neck veins, hypotension | Beck triad of cardiac tamponade | 320 |
| Painful, raised red lesions on pads of fingers/toes | Osler nodes (infective endocarditis, immune complex deposition) | 321 |
| Painless erythematous lesions on palms and soles | Janeway lesions (infective endocarditis, septic emboli/microabscesses) | 321 |
| Splinter hemorrhages in fingernails | Bacterial endocarditis | 321 |
| Retinal hemorrhages with pale centers | Roth spots (bacterial endocarditis) | 321 |
| Telangiectasias, recurrent epistaxis, skin discoloration, arteriovenous malformations, GI bleeding, hematuria | Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) | 324 |
| Polyuria (water diuresis), polydipsia | Primary polydipsia, diabetes insipidus (central, nephrogenic) | 346 |
| No lactation postpartum, absent menstruation, cold intolerance | Sheehan syndrome (postpartum hemorrhage leading to pituitary infarction) | 347 |
| Heat intolerance, weight loss, palpitations | Hyperthyroidism | 348 |
| Cold intolerance, weight gain, brittle hair | Hypothyroidism | 348 |
| Cutaneous/dermal edema due to deposition of mucopolysaccharides in connective tissue | Myxedema (caused by hypothyroidism, Graves disease [pretibial]) | 348 |

| CLINICAL PRESENTATION | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| Facial muscle spasm upon tapping | Chvostek sign (hypocalcemia) | 352 |
| Carpal spasm upon inflation of BP cuff | Trousseau sign (hypocalcemia) | 352 |
| Deep, labored breathing/hyperventilation | Diabetic ketoacidosis (Kussmaul respirations) | 355 |
| Skin hyperpigmentation, orthostatic hypotension, fatigue, weakness, muscle aches, weight loss, GI disturbances | Chronic 1° adrenal insufficiency (Addison disease) → ↑ ACTH, ↑ α-MSH | 357 |
| Shock, altered mental status, vomiting, abdominal pain, weakness, fatigue | Acute adrenal insufficiency (adrenal crisis) | 357 |
| Pancreatic, pituitary, parathyroid tumors | MEN 1 (autosomal dominant *MEN1* mutation) | 360 |
| Thyroid tumors, pheochromocytoma, ganglioneuromatosis, Marfanoid habitus | MEN 2B (autosomal dominant *RET* mutation) | 360 |
| Thyroid and parathyroid tumors, pheochromocytoma | MEN 2A (autosomal dominant *RET* mutation) | 360 |
| Cutaneous flushing, diarrhea, bronchospasm, heart murmur | Carcinoid syndrome (↑ 5-HIAA) | 361 |
| Jaundice, palpable distended non-tender gallbladder | Courvoisier sign (distal malignant obstruction of biliary tree) | 378 |
| Vomiting blood following gastroesophageal lacerations | Mallory-Weiss syndrome (alcohol use disorder, bulimia nervosa) | 387 |
| Dysphagia (esophageal webs), glossitis, iron deficiency anemia | Plummer-Vinson syndrome (may progress to esophageal squamous cell carcinoma) | 387 |
| Enlarged, hard left supraclavicular node | Virchow node (abdominal metastasis) | 389 |
| Hematemesis, melena | Upper GI bleeding (eg, peptic ulcer disease) | 390 |
| Hematochezia | Lower GI bleeding (eg, colonic diverticulosis) | 390 |
| Arthralgias, adenopathy, cardiac and neurological symptoms, diarrhea | Whipple disease (*Tropheryma whipplei*) | 391 |
| Severe RLQ pain with palpation of LLQ | Rovsing sign (acute appendicitis) | 393 |
| Severe RLQ pain with deep tenderness | McBurney sign (acute appendicitis) | 393 |
| Hamartomatous GI polyps, hyperpigmented macules on mouth, feet, hands, genitalia | Peutz-Jeghers syndrome (inherited, benign polyposis can cause bowel obstruction; ↑ cancer risk, mainly GI) | 397 |
| Multiple colon polyps, osteomas/soft tissue tumors, impacted/supernumerary teeth | Gardner syndrome (subtype of FAP) | 397 |
| Severe jaundice in neonate | Crigler-Najjar syndrome (congenital unconjugated hyperbilirubinemia) | 404 |
| Golden brown rings around peripheral cornea | Wilson disease (Kayser-Fleischer rings due to copper accumulation) | 405 |
| Female, fat, fertile, forty | Cholelithiasis (gallstones) | 406 |
| Painless jaundice with enlarged gallbladder | Cancer of the pancreatic head obstructing bile duct | 408 |
| Bluish line on gingiva | Burton line (lead poisoning) | 429 |
| Short stature, café-au-lait spots, thumb/radial defects, ↑ incidence of tumors/leukemia, aplastic anemia | Fanconi anemia (genetic loss of DNA crosslink repair; often progresses to AML) | 431 |
| Red/pink urine, fragile RBCs | Paroxysmal nocturnal hemoglobinuria | 432 |
| Painful blue fingers/toes, hemolytic anemia | Cold agglutinin disease (autoimmune hemolytic anemia caused by *Mycoplasma pneumoniae*, infectious mononucleosis, CLL) | 433 |

| CLINICAL PRESENTATION | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| Petechiae, mucosal bleeding, prolonged bleeding time | Platelet disorders (eg, Glanzmann thrombasthenia, Bernard Soulier, HUS, TTP, ITP) | 437 |
| Fever, night sweats, weight loss | B symptoms of malignancy | 438 |
| Skin patches/plaques, Pautrier microabscesses, atypical T cells | Mycosis fungoides (cutaneous T-cell lymphoma) or Sézary syndrome (mycosis fungoides + malignant T cells in blood) | 439 |
| Neonate with arm paralysis following difficult birth, arm in "waiter's tip" position | Erb-Duchenne palsy (superior trunk [C5–C6] brachial plexus injury) | 458 |
| Anterior drawer sign ⊕ | Anterior cruciate ligament injury | 464 |
| Bone pain, bone enlargement, arthritis | Osteitis deformans (Paget disease of bone, ↑ osteoblastic and osteoclastic activity) | 475 |
| Swollen, hard, painful finger joints in an elderly individual, pain worse with activity | Osteoarthritis (osteophytes on PIP [Bouchard nodes], DIP [Heberden nodes]) | 478 |
| Sudden swollen/painful big toe joint, tophi | Gout/podagra (hyperuricemia) | 479 |
| Dry eyes, dry mouth, arthritis | Sjögren syndrome (autoimmune destruction of exocrine glands) | 480 |
| Urethritis, conjunctivitis, arthritis in a male | Reactive arthritis associated with HLA-B27 | 481 |
| "Butterfly" facial rash, arthritis, cytopenia, and fever in a young female | Systemic lupus erythematosus | 482 |
| Cervical lymphadenopathy, desquamating rash, coronary aneurysms, red conjunctivae and tongue, hand-foot changes | Kawasaki disease (mucocutaneous lymph node syndrome, treat with IVIG and aspirin) | 484 |
| Palpable purpura on buttocks/legs, joint pain, abdominal pain (child), hematuria | Immunoglobulin A vasculitis (Henoch-Schönlein purpura, affects skin and kidneys) | 485 |
| Painful fingers/toes changing color from white to blue to red with cold or stress | Raynaud phenomenon (vasospasm in extremities) | 486 |
| Dark purple skin/mouth nodules in a patient with AIDS | Kaposi sarcoma, associated with HHV-8 | 492 |
| Pruritic, purple, polygonal planar papules and plaques (6 P's) | Lichen planus | 496 |
| Ataxia, nystagmus, vertigo, dysarthria | Cerebellar lesion (lateral affects voluntary movement of extremities; medial affects axial and proximal movement) | 515 |
| Dorsiflexion of large toe with fanning of other toes upon plantar scrape | Babinski sign (UMN lesion) | 527 |
| Hyperphagia, hypersexuality, hyperorality | Klüver-Bucy syndrome (bilateral amygdala lesion) | 528 |
| Resting tremor, athetosis, chorea | Basal ganglia lesion | 528 |
| Lucid interval after traumatic brain injury | Epidural hematoma (middle meningeal artery rupture; branch of maxillary artery) | 531 |
| "Worst headache of my life" | Subarachnoid hemorrhage | 531 |
| Dysphagia, hoarseness, ↓ gag reflex, nystagmus, ipsilateral Horner syndrome | Lateral medullary syndrome (posterior inferior cerebellar artery lesion) | 533 |
| Resting tremor, rigidity, akinesia, postural instability, shuffling gait, micrographia | Parkinson disease (loss of dopaminergic neurons in substantia nigra pars compacta) | 538 |
| Chorea, dementia, caudate degeneration | Huntington disease (autosomal dominant CAG repeat expansion) | 538 |

| CLINICAL PRESENTATION | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| Urinary incontinence, gait apraxia, cognitive dysfunction | Normal pressure hydrocephalus | 540 |
| Nystagmus, intention tremor, scanning speech, bilateral internuclear ophthalmoplegia | Multiple sclerosis | 541 |
| Rapidly progressive limb weakness that ascends following GI/upper respiratory infection | Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy) | 542 |
| Café-au-lait spots, Lisch nodules (iris hamartoma), cutaneous neurofibromas, pheochromocytomas, optic gliomas | Neurofibromatosis type I | 543 |
| Vascular birthmark (port-wine stain) of the face | Nevus flammeus (benign, but associated with Sturge-Weber syndrome) | 543 |
| Renal cell carcinoma (bilateral), hemangioblastomas, angiomatosis, pheochromocytoma | von Hippel-Lindau disease (deletion of *VHL* gene on chromosome 3p) | 543 |
| Bilateral vestibular schwannomas | Neurofibromatosis type 2 | 543 |
| Hyperreflexia, hypertonia, Babinski sign present | UMN damage | 547 |
| Hyporeflexia, hypotonia, atrophy, fasciculations | LMN damage | 547 |
| Flaccid limb weakness, fasciculations, atrophy, bulbar palsy | UMN and LMN deficits | 548 |
| Staggering gait, frequent falls, nystagmus, hammer toes, diabetes mellitus, hypertrophic cardiomyopathy | Friedreich ataxia | 549 |
| Unilateral facial drooping involving forehead | LMN facial nerve (CN VII) palsy; UMN lesions spare the forehead | 550 |
| Episodic vertigo, tinnitus, sensorineural hearing loss | Ménière disease | 552 |
| Ptosis, miosis, anhidrosis | Horner syndrome (sympathetic chain lesion) | 559 |
| Conjugate horizontal gaze palsy, horizontal diplopia | Internuclear ophthalmoplegia (damage to MLF; may be unilateral or bilateral) | 563 |
| "Waxing and waning" level of consciousness (acute onset), ↓ attention span, ↓ level of arousal | Delirium (usually 2° to other cause) | 581 |
| Polyuria, renal tubular acidosis type II, growth retardation, electrolyte imbalances, hypophosphatemic rickets | Fanconi syndrome (multiple combined dysfunction of the proximal convoluted tubule) | 610 |
| Periorbital and/or peripheral edema, proteinuria (> 3.5g/day), hypoalbuminemia, hypercholesterolemia | Nephrotic syndrome | 619 |
| Hereditary nephritis, sensorineural hearing loss, retinopathy, lens dislocation | Alport syndrome (mutation in type IV collagen) | 620 |
| Wilms tumor, macroglossia, organomegaly, hemihyperplasia, omphalocele | Beckwith-Wiedemann syndrome (*WT2* mutation) | 629 |
| Streak ovaries, congenital heart disease, horseshoe kidney, cystic hygroma, short stature, webbed neck, lymphedema | Turner syndrome (45,XO) | 661 |
| Red, itchy, swollen rash of nipple/areola | Paget disease of the breast (sign of underlying neoplasm) | 674 |
| Ovarian fibroma, ascites, pleural effusion | Meigs syndrome | 671 |
| Fibrous plaques in tunica albuginea of penis with abnormal curvature | Peyronie disease (connective tissue disorder) | 675 |
| Hypoxemia, polycythemia, hypercapnia | Chronic bronchitis (hypertrophy and hyperplasia of mucous cells, "blue bloater") | 698 |

| CLINICAL PRESENTATION | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| Pink complexion, dyspnea, hyperventilation | Emphysema ("pink puffer," centriacinar [smoking] or panacinar [$\alpha_1$-antitrypsin deficiency]) | 698 |
| Bilateral hilar adenopathy, uveitis | Sarcoidosis (noncaseating granulomas) | 700 |

## ▸ CLASSIC LABS/FINDINGS

| LAB/DIAGNOSTIC FINDING | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| Colonies of mucoid *Pseudomonas* in lungs | Cystic fibrosis (autosomal recessive mutation in *CFTR* gene → fat-soluble vitamin deficiency and mucous plugs) | 60 |
| ↓ AFP in amniotic fluid/maternal serum | Down syndrome, Edwards syndrome | 63 |
| ↑ β-hCG, ↓ PAPP-A on first trimester screening | Down syndrome | 63 |
| ↑ serum homocysteine, ↑ mehtylmalonic acid, ↓ folate | Vitamin $B_{12}$ deficiency | 69 |
| Anti-histone antibodies | Drug-induced SLE (eg, hydralazine, isoniazid, phenytoin, TNF-α inhibitors) | 115, 501 |
| ↓ T cells, ↓ PTH, ↓ $Ca^{2+}$, absent thymic shadow on CXR | Thymic aplasia (DiGeorge syndrome, velocardiofacial syndrome) | 116 |
| Large granules in phagocytes, immunodeficiency | Chédiak-Higashi disease (congenital failure of phagolysosome formation) | 117 |
| Recurrent infections, eczema, thrombocytopenia | Wiskott-Aldrich syndrome | 117 |
| Optochin sensitivity | Sensitive: *S pneumoniae*; resistant: viridans streptococci (*S mutans*, *S sanguis*) | 134 |
| Novobiocin response | Sensitive: *S epidermidis*; resistant: *S saprophyticus* | 134 |
| Bacitracin response | Sensitive: *S pyogenes* (group A); resistant: *S agalactiae* (group B) | 134 |
| Branching gram ⊕ rods with sulfur granules | *Actinomyces israelii* | 139 |
| Hilar lymphadenopathy, peripheral granulomatous lesion in middle or lower lung lobes (can calcify) | Ghon complex (1° TB: *Mycobacterium* bacilli) | 140 |
| "Thumb sign" on lateral neck x-ray | Epiglottitis (*Haemophilus influenzae*) | 142 |
| Bacteria-covered vaginal epithelial cells | "Clue cells" (*Gardnerella vaginalis*) | 148 |
| Dilated cardiomyopathy with apical atrophy | Chagas disease (*Trypanosoma cruzi*) | 158 |
| Atypical lymphocytes, heterophile antibodies | Infectious mononucleosis (EBV infection) | 165 |
| Eosinophilic intranuclear inclusions with perinuclear halo | Cells infected by herpesviruses (eg, HSV, VZV, CMV) | 165, 166 |
| "Steeple" sign on frontal CXR | Croup (parainfluenza virus) | 170 |
| Eosinophilic inclusion bodies in cytoplasm of hippocampal and cerebellar neurons | Negri bodies of rabies | 171 |
| Ring-enhancing brain lesion on CT/MRI in AIDS | *Toxoplasma gondii*, CNS lymphoma | 177 |
| Psammoma bodies | Meningiomas, papillary thyroid carcinoma, mesothelioma, papillary serous carcinoma of the endometrium and ovary | 228 |

| LAB/DIAGNOSTIC FINDING | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| "Delta wave" on ECG, short PR interval, supraventricular tachycardia | Wolff-Parkinson-White syndrome (bundle of Kent bypasses AV node) | 315 |
| "Boot-shaped" heart on x-ray | Tetralogy of Fallot (due to RVH) | 306 |
| Rib notching (inferior surface, on x-ray) | Coarctation of the aorta | 307 |
| Granuloma with giant cells after pharyngeal infection | Aschoff bodies (rheumatic fever) | 322 |
| Electrical alternans (alternating amplitude on ECG) | Cardiac tamponade | 320 |
| Enlarged thyroid cells with ground-glass nuclei with central clearing | "Orphan Annie" eyes nuclei (papillary carcinoma of the thyroid) | 351 |
| "Brown" tumor of bone | Hyperparathyroidism or osteitis fibrosa cystica (deposited hemosiderin from hemorrhage gives brown color) | 353, 476 |
| Hypertension, hypokalemia, metabolic alkalosis | 1° hyperaldosteronism (eg, Conn syndrome) | 358 |
| Mucin-filled cell with peripheral nucleus | "Signet ring" (gastric carcinoma) | 389 |
| Anti-transglutaminase/anti-gliadin/anti-endomysial antibodies | Celiac disease (diarrhea, weight loss) | 391 |
| Narrowing of bowel lumen on barium x-ray | "String sign" (Crohn disease) | 392 |
| "Lead pipe" appearance of colon on abdominal imaging | Ulcerative colitis (loss of haustra) | 392 |
| Thousands of polyps on colonoscopy | Familial adenomatous polyposis (autosomal dominant, mutation of APC gene) | 397 |
| "Apple core" lesion on barium enema x-ray | Colorectal cancer (usually left-sided) | 398 |
| Eosinophilic cytoplasmic inclusion in liver cell | Mallory body (alcoholic liver disease) | 401 |
| Triglyceride accumulation in liver cell vacuoles | Fatty liver disease (alcoholic or metabolic syndrome) | 401 |
| Anti-smooth muscle antibodies (ASMAs), anti-liver/kidney microsomal-1 (anti-LKM1) antibodies | Autoimmune hepatitis | 401 |
| "Nutmeg" appearance of liver | Chronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome | 402 |
| Antimitochondrial antibodies (AMAs) | 1° biliary cholangitis (female, cholestasis, portal hypertension) | 405 |
| Low serum ceruloplasmin | Wilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation) | 405 |
| Migratory thrombophlebitis (leading to migrating DVTs and vasculitis) | Trousseau syndrome (adenocarcinoma of pancreas or lung) | 408 |
| Hypersegmented neutrophils | Megaloblastic anemia ($B_{12}$ deficiency: neurologic symptoms; folate deficiency: no neurologic symptoms) | 416 |
| Basophilic nuclear remnants in RBCs | Howell-Jolly bodies (due to splenectomy or nonfunctional spleen) | 426 |
| Basophilic stippling of RBCs | Lead poisoning or sideroblastic anemia | 426 |
| Hypochromic, microcytic anemia | Iron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present) | 427, 428 |
| "Hair on end" ("crew cut") appearance on x-ray | β-thalassemia, sickle cell disease (marrow expansion) | 428, 432 |
| Anti-GpIIb/IIIa antibodies | Immune thrombocytopenia | 436 |
| High level of D-dimers | DVT, DIC | 437, 695 |

| LAB/DIAGNOSTIC FINDING | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| Giant B cells with bilobed nuclei with prominent inclusions ("owl's eye") | Reed-Sternberg cells (Hodgkin lymphoma) | 438 |
| Sheets of medium-sized lymphoid cells with scattered pale, tingible body–laden macrophages ("starry sky" histology) | Burkitt lymphoma (t[8:14] c-*myc* activation, associated with EBV; "starry sky" made up of malignant cells) | 439 |
| Lytic ("punched-out") bone lesions on x-ray | Multiple myeloma | 440 |
| Monoclonal spike on serum protein electrophoresis | ▪ Multiple myeloma (usually IgG or IgA)<br>▪ Waldenström macroglobulinemia (IgM)<br>▪ Monoclonal gammopathy of undetermined significance | 440 |
| Stacks of RBCs | Rouleaux formation (high ESR, multiple myeloma) | 440 |
| Azurophilic peroxidase ⊕ granular inclusions in granulocytes and myeloblasts | Auer rods (APL) | 442 |
| WBCs that look "smudged" | CLL | 442 |
| "Tennis racket"-shaped cytoplasmic organelles (EM) in Langerhans cells | Birbeck granules (Langerhans cell histiocytosis) | 444 |
| "Soap bubble" in femur or tibia on x-ray | Giant cell tumor of bone (generally benign) | 476 |
| Raised periosteum (creating a "Codman triangle") | Aggressive bone lesion (eg, osteosarcoma, Ewing sarcoma) | 477 |
| "Onion skin" periosteal reaction | Ewing sarcoma (malignant small blue cell tumor) | 477 |
| Anti-IgG antibodies | Rheumatoid arthritis (systemic inflammation, joint pannus, boutonniere and swan neck deformities) | 478 |
| Rhomboid crystals, ⊕ birefringent | Pseudogout (calcium pyrophosphate dihydrate crystals) | 479 |
| Needle-shaped, ⊖ birefringent crystals | Gout (monosodium urate crystals) | 479 |
| ↑ uric acid levels | Gout, Lesch-Nyhan syndrome, tumor lysis syndrome, loop and thiazide diuretics | 479 |
| "Bamboo spine" on x-ray | Ankylosing spondylitis (chronic inflammatory arthritis: HLA-B27) | 481 |
| Antinuclear antibodies (ANAs: anti-Smith and anti-dsDNA) | SLE (type III hypersensitivity) | 482 |
| Antineutrophil cytoplasmic antibodies (ANCAs) | Microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (MPO-ANCA/p-ANCA); granulomatosis with polyangiitis (PR3-ANCA/c-ANCA); primary sclerosing cholangitis (MPO-ANCA/p-ANCA) | 485 |
| Anticentromere antibodies | Scleroderma (CREST syndrome) | 487 |
| Anti-topoisomerase antibodies | Diffuse scleroderma | 487 |
| Anti-desmoglein (anti-desmosome) antibodies | Pemphigus vulgaris (blistering) | 494 |
| Keratin pearls on a skin biopsy | Squamous cell carcinoma | 498 |
| ↑ AFP in amniotic fluid/maternal serum | Dating error, anencephaly, spina bifida (open neural tube defects) | 505 |
| Bloody or yellow tap on lumbar puncture | Xanthochromia (due to subarachnoid hemorrhage) | 531 |
| Eosinophilic cytoplasmic inclusion in neuron | Lewy body (Parkinson disease and Lewy body dementia) | 538, 539 |
| Extracellular amyloid deposition in gray matter of brain | Senile plaques (Alzheimer disease) | 538 |

| LAB/DIAGNOSTIC FINDING | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| Depigmentation of neurons in substantia nigra | Parkinson disease (basal ganglia disorder: rigidity, resting tremor, bradykinesia) | 538 |
| Protein aggregates in neurons from hyperphosphorylation of tau protein | Neurofibrillary tangles (Alzheimer disease) and Pick bodies (Pick disease) | 538 |
| Silver-staining spherical aggregation of tau proteins in neurons | Pick bodies (frontotemporal dementia: progressive dementia, changes in personality) | 538 |
| Pseudopalisading pleomorphic tumor cells on brain biopsy | Glioblastoma multiforme | 544 |
| Circular grouping of dark tumor cells surrounding pale neurofibrils | Homer-Wright rosettes (neuroblastoma, medulloblastoma) | 546 |
| "Waxy" casts with very low urine flow | Chronic end-stage renal disease | 618 |
| WBC casts in urine | Acute pyelonephritis, transplant rejection, tubulointerstitial inflammation | 618 |
| RBC casts in urine | Glomerulonephritis | 618 |
| "Tram-track" appearance of capillary loops of glomerular basement membranes on light microscopy | Membranoproliferative glomerulonephritis | 620 |
| Anti–glomerular basement membrane antibodies | Goodpasture syndrome (glomerulonephritis and hemoptysis) | 620 |
| Cellular crescents in Bowman capsule | Rapidly progressive (crescentic) glomerulonephritis | 620 |
| "Wire loop" glomerular capillary appearance on light microscopy | Diffuse proliferative glomerulonephritis (usually seen with lupus) | 620 |
| Linear appearance of IgG deposition on glomerular and alveolar basement membranes | Goodpasture syndrome | 620 |
| "Lumpy bumpy" appearance of glomeruli on immunofluorescence | Poststreptococcal glomerulonephritis (due to deposition of IgG, IgM, and C3) | 620 |
| Necrotizing vasculitis (lungs) and necrotizing glomerulonephritis | Granulomatosis with polyangiitis (PR3-ANCA/c-ANCA) and Goodpasture syndrome (anti–basement membrane antibodies) | 620 |
| Nodular hyaline deposits in glomeruli | Kimmelstiel-Wilson nodules (diabetic nephropathy) | 621 |
| Podocyte fusion or "effacement" on electron microscopy | Minimal change disease (child with nephrotic syndrome) | 621 |
| "Spikes" on basement membrane, "dome-like" subepithelial deposits | Membranous nephropathy (nephrotic syndrome) | 621 |
| Thyroid-like appearance of kidney | Chronic pyelonephritis (usually due to recurrent infections) | 624 |
| Granular casts in urine | Acute tubular necrosis (eg, ischemia or toxic injury) | 626 |
| hCG elevated | Multiple gestations, hydatidiform moles, choriocarcinomas, Down syndrome | 658 |
| Dysplastic squamous cervical cells with "raisinoid" nuclei and hyperchromasia | Koilocytes (HPV: predisposes to cervical cancer) | 669 |
| Sheets of uniform "fried egg" cells, ↑ hCG, ↑ LDH | Dysgerminoma | 671 |
| Disarrayed granulosa cells arranged around collections of eosinophilic fluid | Call-Exner bodies (granulosa cell tumor of the ovary) | 671 |
| "Chocolate cyst" of ovary | Endometriosis (frequently involves both ovaries) | 672 |
| Mammary gland ("blue domed") cyst | Fibrocystic change of the breast | 673 |

| LAB/DIAGNOSTIC FINDING | DIAGNOSIS/DISEASE | PAGE |
|---|---|---|
| Glomerulus-like structure surrounding vessel in germ cells | Schiller-Duval bodies (yolk sac tumor) | 671 |
| Rectangular, crystal-like, cytoplasmic inclusions in Leydig cells | Reinke crystals (Leydig cell tumor) | 677 |
| Thrombi made of white/red layers | Lines of Zahn (arterial thrombus, layers of platelets/RBCs) | 696 |
| Hexagonal, double-pointed, needle-like crystals in bronchial secretions | Bronchial asthma (Charcot-Leyden crystals: eosinophilic granules) | 698 |
| Desquamated epithelium casts in sputum | Curschmann spirals (bronchial asthma; can result in whorled mucous plugs) | 698 |
| "Honeycomb lung" on x-ray or CT | Idiopathic pulmonary fibrosis | 700 |
| Iron-containing nodules in alveolar septum | Ferruginous bodies (asbestosis: ↑ chance of lung cancer) | 701 |
| Bronchogenic apical lung tumor on imaging | Pancoast tumor (can compress cervical sympathetic chain and cause Horner syndrome) | 709 |

## ▸ CLASSIC/RELEVANT TREATMENTS

| CONDITION | COMMON TREATMENT(S) | PAGE |
|---|---|---|
| Ethylene glycol/methanol intoxication | Fomepizole (alcohol dehydrogenase inhibitor) | 72 |
| Chronic hepatitis B or C | IFN-α (HBV and HCV); ribavirin, simeprevir, sofosbuvir (HCV) | 121, 204 |
| *Streptococcus bovis* | Penicillin prophylaxis; evaluation for colon cancer if linked to endocarditis | 137 |
| *Clostridium botulinum* | Human botulinum immunoglobulin | 138 |
| *Clostridium tetani* | Antitoxin and wound debridement | 138 |
| *Clostridium difficile* | Oral metronidazole; if refractory, oral vancomycin. Refractory cases: repeat regimen or fecal microbiota transplant | 138 |
| *Haemophilus influenzae* (B) | Amoxicillin ± clavulanate (mucosal infections), ceftriaxone (meningitis), rifampin (prophylaxis) | 142 |
| *Neisseria gonorrhoeae* | Ceftriaxone (add azithromycin or doxycycline to cover likely concurrent C *trachomatis*) | 142 |
| *Neisseria meningitidis* | Penicillin/ceftriaxone, rifampin/ciprofloxacin/ceftriaxone (prophylaxis) | 142 |
| *Legionella pneumophila* | Macrolides (eg, azithromycin or fluoroquinolones) | 143 |
| *Pseudomonas aeruginosa* | Piperacillin-tazobactam, cephalosporins, monobactams, fluoroquinolones, carbapenems | 143 |
| *Treponema pallidum* | Penicillin G | 147 |
| *Chlamydia trachomatis* | Azithromycin or doxycycline (+ ceftriaxone for gonorrhea coinfection), oral erythromycin to treat chlamydial conjunctivitis in infants | 148 |

| CONDITION | COMMON TREATMENT(S) | PAGE |
|---|---|---|
| *Candida albicans* | Topical azoles (vaginitis); nystatin, fluconazole, caspofungin (oral); fluconazole, caspofungin, amphotericin B (esophageal or systemic) | 153 |
| *Cryptococcus neoformans* | Induction with amphotericin B and flucytosine, maintenance with fluconazole (in AIDS patients) | 153 |
| *Sporothrix schenckii* | Itraconazole, oral potassium iodide | 154 |
| *Pneumocystis jirovecii* | TMP-SMX (prophylaxis and treatment in immunosuppressed patients, CD4 < 200/mm$^3$) | 154 |
| *Toxoplasma gondii* | Sulfadiazine + pyrimethamine | 156 |
| Malaria | Chloroquine, mefloquine, atovaquone/proguanil (for blood schizont), primaquine (for liver hypnozoite) | 157 |
| *Trichomonas vaginalis* | Metronidazole (patient and partner[s]) | 158 |
| *Streptococcus pyogenes* | Penicillin prophylaxis | 187 |
| *Streptococcus pneumoniae* | Penicillin/cephalosporin (systemic infection, pneumonia), vancomycin (meningitis) | 187, 190 |
| *Staphylococcus aureus* | MSSA: nafcillin, oxacillin, dicloxacillin (antistaphylococcal penicillins); MRSA: vancomycin, daptomycin, linezolid, ceftaroline | 188, 190, 198 |
| Enterococci | Vancomycin, aminopenicillins/cephalosporins. VRE: daptomycin, linezolid, tigecycline, streptogramins | 189, 198 |
| *Rickettsia rickettsii* | Doxycycline, chloramphenicol | 192 |
| *Mycobacterium tuberculosis* | RIPE (rifampin, isoniazid, pyrazinamide, ethambutol) | 196 |
| UTI prophylaxis | TMP-SMX | 198 |
| Influenza | Oseltamivir, zanamivir | 201 |
| CMV | Ganciclovir, foscarnet, cidofovir | 202 |
| Patent ductus arteriosus | Close with indomethacin; keep open with PGE analogs | 291 |
| Stable angina | Sublingual nitroglycerin | 312 |
| Hypercholesterolemia | Statin (first-line) | 328 |
| Hypertriglyceridemia | Fibrate | 328 |
| Arrhythmia in damaged cardiac tissue | Class IB antiarrhythmic (lidocaine, mexiletine) | 330 |
| Prolactinoma | Cabergoline/bromocriptine (dopamine agonists) | 338 |
| Diabetes insipidus | Desmopressin (central); hydrochlorothiazide, indomethacin, amiloride (nephrogenic) | 346 |
| SIADH | Fluid restriction, IV hypertonic saline, conivaptan/tolvaptan, demeclocycline | 346 |
| Diabetic ketoacidosis/hyperosmolar hyperglycemic state | Fluids, insulin, $K^+$ | 355 |
| Pheochromocytoma | $\alpha$-antagonists (eg, phenoxybenzamine) | 359 |
| Carcinoid syndrome | Octreotide, telotristat | 361 |
| Diabetes mellitus type 1 | Dietary intervention (low carbohydrate) + insulin replacement | 362 |
| Diabetes mellitus type 2 | Dietary intervention, oral hypoglycemics, and insulin (if refractory) | 362 |

| CONDITION | COMMON TREATMENT(S) | PAGE |
|---|---|---|
| Crohn disease | Corticosteroids, infliximab, azathioprine | 392 |
| Ulcerative colitis | 5-ASA preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy | 392 |
| Sickle cell disease | Hydroxyurea (↑ fetal hemoglobin) | 432 |
| Chronic myelogenous leukemia | BCR-ABL tyrosine kinase inhibitors (eg, imatinib) | 442 |
| Acute promyelocytic leukemia (M3) | All-*trans* retinoic acid, arsenic trioxide | 442 |
| Drug of choice for anticoagulation in pregnancy | Low-molecular-weight heparin | 445 |
| Immediate anticoagulation | Heparin | 445 |
| Long-term anticoagulation | Warfarin, dabigatran, direct factor Xa inhibitors | 446 |
| Heparin reversal | Protamine sulfate | 447 |
| Warfarin reversal | Vitamin K (slow) +/– fresh frozen plasma or prothrombin complex concentrate (rapid) | 447 |
| Dabigatran reversal | Idarucizumab | 447 |
| Direct factor Xa inhibitor reversal | Andexanet alfa | 447 |
| HER2 ⊕ breast cancer | Trastuzumab | 452 |
| Hemorrhagic cystitis from cyclophosphamide/ifosfamide | Mesna | 453 |
| Nephrotoxicity from platinum compounds | Amifostine | 453 |
| Cardiotoxicity from anthracyclines | Dexrazoxane | 453 |
| Myelosuppression from methotrexate | Leucovorin | 453 |
| Osteoporosis | Calcium/vitamin D supplementation (prophylaxis); bisphosphonates, PTH analogs, SERMs, calcitonin, denosumab (treatment) | 474 |
| Osteomalacia/rickets | Vitamin D supplementation | 475 |
| Chronic gout | Xanthine oxidase inhibitors (eg, allopurinol, febuxostat); pegloticase; probenecid | 479 |
| Acute gout attack | NSAIDs, colchicine, glucocorticoids | 479 |
| Buerger disease | Smoking cessation | 484 |
| Kawasaki disease | IVIG, aspirin | 484 |
| Temporal arteritis | High-dose glucocorticoids | 484 |
| Granulomatosis with polyangiitis | Cyclophosphamide, glucocorticoids | 485 |
| Neural tube defect prevention | Prenatal folic acid | 505 |
| Migraine | Abortive therapies (eg, sumatriptan, NSAIDs); prophylaxis (eg, propranolol, topiramate, anti-CGRP antibodies, amitriptyline) | 536 |
| Multiple sclerosis | Disease-modifying therapies (eg, β-interferon, glatiramer, natalizumab); for acute flares, use IV steroids | 541 |
| Tonic-clonic seizures | Levetiracetam, phenytoin, valproate, carbamazepine | 564 |
| Absence seizures | Ethosuximide | 564 |
| Trigeminal neuralgia (tic douloureux) | Carbamazepine | 536 |

| CONDITION | COMMON TREATMENT(S) | PAGE |
|---|---|---|
| Malignant hyperthermia | Dantrolene | 572 |
| Anorexia | Nutrition, psychotherapy, SSRIs | 590 |
| Bulimia nervosa | Nutrition rehabilitation, psychotherapy, SSRIs | 590 |
| Alcohol use disorder | Disulfiram, acamprosate, naltrexone, supportive care | 595 |
| ADHD | Methylphenidate, amphetamines, behavioral therapy, atomoxetine, guanfacine, clonidine | 580, 596 |
| Alcohol withdrawal | Long-acting benzodiazepines | 596 |
| Bipolar disorder | Mood stabilizers (eg, lithium, valproic acid, carbamazepine), atypical antipsychotics | 596 |
| Depression | SSRIs (first-line) | 596 |
| Generalized anxiety disorder | SSRIs, SNRIs (first line); buspirone (second line) | 596 |
| Schizophrenia | Atypical antipsychotics | 583, 596 |
| Hyperaldosteronism | Spironolactone | 632 |
| Benign prostatic hyperplasia | $\alpha_1$-antagonists, 5$\alpha$-reductase inhibitors, PDE-5 inhibitors, TURP | 678 |
| Infertility | Leuprolide, GnRH (pulsatile), clomiphene | 680 |
| Breast cancer in postmenopausal woman | Aromatase inhibitor (anastrozole) | 680 |
| ER/PR ⊕ breast cancer | Tamoxifen | 680 |
| Uterine fibroids | Leuprolide, GnRH (continuous) | 680 |
| Medical abortion | Mifepristone | 681 |
| Prostate adenocarcinoma | Flutamide, GnRH (continuous), degarelix, ketoconazole | 680, 682 |
| Erectile dysfunction | Sildenafil | 711 |
| Pulmonary arterial hypertension (idiopathic) | Sildenafil, bosentan, epoprostenol, iloprost | 711 |

## ▸ KEY ASSOCIATIONS

| DISEASE/FINDING | MOST COMMON/IMPORTANT ASSOCIATIONS | PAGE |
|---|---|---|
| Mitochondrial inheritance | Disease occurs in both males and females, inherited through females only | 59 |
| Intellectual disability | Down syndrome, fragile X syndrome | 62, 63 |
| Vitamin deficiency (USA) | Folate (pregnant women are at high risk; body stores only 3- to 4-month supply; prevents neural tube defects) | 68 |
| Lysosomal storage disease | Gaucher disease | 88 |
| Bacterial meningitis (> 6 months old) | *S pneumoniae* | 180 |
| Bacterial meningitis (newborns and kids) | Group B streptococcus/*E coli*/*Listeria monocytogenes* (newborns) | 180 |

| DISEASE/FINDING | MOST COMMON/IMPORTANT ASSOCIATIONS | PAGE |
|---|---|---|
| HLA-DR3 | Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis (also associated with HLA-DR5), Addison disease | 100 |
| HLA-DR4 | Diabetes mellitus type 1, rheumatoid arthritis, Addison disease | 100 |
| Bacteria associated with gastritis, peptic ulcer disease, and gastric malignancies (eg, adenocarcinoma, MALToma) | *H pylori* | 146 |
| Opportunistic respiratory infection in AIDS | *Pneumocystis jirovecii* pneumonia | 154 |
| Helminth infection (US) | *Enterobius vermicularis* | 159 |
| Viral encephalitis affecting temporal lobe | HSV-1 | 164 |
| Infection 2° to blood transfusion | Hepatitis C | 173 |
| Food poisoning (exotoxin mediated) | *S aureus*, *B cereus* | 178 |
| Osteomyelitis | *S aureus* (most common overall) | 180 |
| Osteomyelitis in sickle cell disease | *Salmonella* | 180 |
| Osteomyelitis with IV drug use | *S aureus*, *Pseudomonas*, *Candida* | 180 |
| UTI | *E coli*, *Staphylococcus saprophyticus* (young women) | 181 |
| Sexually transmitted disease | *C trachomatis* (usually coinfected with *N gonorrhoeae*) | 184 |
| Nosocomial pneumonia | *S aureus*, *Pseudomonas*, *Klebsiella*, *Acinetobacter* | 185 |
| Pelvic inflammatory disease | *C trachomatis*, *N gonorrhoeae* | 185 |
| Metastases to bone | Prostate, breast > kidney, thyroid, lung | 224 |
| Metastases to brain | Lung > breast > melanoma, colon, kidney | 224 |
| Metastases to liver | Colon >> stomach > pancreas | 224 |
| S3 heart sound | ↑ ventricular filling pressure (eg, mitral regurgitation, HF), common in dilated ventricles | 296 |
| S4 heart sound | Stiff/hypertrophic ventricle (aortic stenosis, restrictive cardiomyopathy) | 296 |
| Constrictive pericarditis | TB (developing world); idiopathic, viral illness (developed world) | 296, 320 |
| Holosystolic murmur | VSD, tricuspid regurgitation, mitral regurgitation | 299 |
| Ejection click | Aortic stenosis | 300 |
| Mitral valve stenosis | Rheumatic heart disease | 300 |
| Opening snap | Mitral stenosis | 300 |
| Heart murmur, congenital | Mitral valve prolapse | 300 |
| Chronic arrhythmia | Atrial fibrillation (associated with high risk of emboli) | 316 |
| Cyanosis (early; less common) | Tetralogy of Fallot, transposition of great vessels, truncus arteriosus, total anomalous pulmonary venous return, tricuspid atresia | 306 |
| Late cyanotic shunt (uncorrected left to right becomes right to left) | Eisenmenger syndrome (caused by ASD, VSD, PDA; results in pulmonary hypertension/polycythemia) | 307 |
| Congenital cardiac anomaly | VSD | 307 |

| DISEASE/FINDING | MOST COMMON/IMPORTANT ASSOCIATIONS | PAGE |
|---|---|---|
| Hypertension, 2° | Renal artery stenosis, chronic kidney disease (eg, polycystic kidney disease, diabetic nephropathy), hyperaldosteronism | 308 |
| Aortic aneurysm, thoracic | Marfan syndrome (idiopathic cystic medial degeneration) | 310 |
| Aortic aneurysm, abdominal | Atherosclerosis, smoking is major risk factor | 310 |
| Aortic aneurysm, ascending or arch | 3° syphilis (syphilitic aortitis), vasa vasorum destruction | 310 |
| Sites of atherosclerosis | Abdominal aorta > coronary artery > popliteal artery > carotid artery | 310 |
| Aortic dissection | Hypertension | 311 |
| Right heart failure due to a pulmonary cause | Cor pulmonale | 319 |
| Heart valve in bacterial endocarditis | Mitral > aortic (rheumatic fever), tricuspid (IV drug abuse) | 321 |
| Endocarditis presentation associated with bacterium | *S aureus* (acute, IVDA, tricuspid valve), viridans streptococci (subacute, dental procedure), *S bovis* (colon cancer), culture negative (*Coxiella*, *Bartonella*, HACEK) | 321 |
| Temporal arteritis | Risk of ipsilateral blindness due to occlusion of ophthalmic artery; polymyalgia rheumatica | 484 |
| Recurrent inflammation/thrombosis of small/medium vessels in extremities | Buerger disease (strongly associated with tobacco) | 484 |
| Cardiac 1° tumor (kids) | Rhabdomyoma, often seen in tuberous sclerosis | 324 |
| Cardiac tumor (adults) | Metastasis, myxoma (90% in left atrium; "ball valve") | 324 |
| Congenital adrenal hyperplasia, hypotension | 21-hydroxylase deficiency | 343 |
| Hypopituitarism | Pituitary adenoma (usually benign tumor) | 347 |
| Congenital hypothyroidism (cretinism) | Thyroid dysgenesis/dyshormonogenesis, iodine deficiency | 349 |
| Thyroid cancer | Papillary carcinoma (childhood irradiation) | 351 |
| Hypoparathyroidism | Accidental excision during thyroidectomy | 352 |
| 1° hyperparathyroidism | Adenomas, hyperplasia, carcinoma | 353 |
| 2° hyperparathyroidism | Hypocalcemia of chronic kidney disease | 353 |
| Cushing syndrome | ▪ Iatrogenic (from corticosteroid therapy)<br>▪ Adrenocortical adenoma (secretes excess cortisol)<br>▪ ACTH-secreting pituitary adenoma (Cushing disease)<br>▪ Paraneoplastic (due to ACTH secretion by tumors) | 356 |
| 1° hyperaldosteronism | Adrenal hyperplasia or adenoma | 358 |
| Tumor of the adrenal medulla (kids) | Neuroblastoma (malignant) | 358 |
| Tumor of the adrenal medulla (adults) | Pheochromocytoma (usually benign) | 359 |
| Refractory peptic ulcers and high gastrin levels | Zollinger-Ellison syndrome (gastrinoma of duodenum or pancreas), associated with MEN1 | 360, 361 |
| Esophageal cancer | Squamous cell carcinoma (worldwide); adenocarcinoma (US) | 388 |
| Acute gastric ulcer associated with CNS injury | Cushing ulcer (↑ intracranial pressure stimulates vagal gastric $H^+$ secretion) | 389 |
| Acute gastric ulcer associated with severe burns | Curling ulcer (greatly reduced plasma volume results in sloughing of gastric mucosa) | 389 |

| DISEASE/FINDING | MOST COMMON/IMPORTANT ASSOCIATIONS | PAGE |
|---|---|---|
| Bilateral ovarian metastases from gastric carcinoma | Krukenberg tumor (mucin-secreting signet ring cells) | 389 |
| Chronic atrophic gastritis (autoimmune) | Predisposition to gastric carcinoma (can also cause pernicious anemia) | 389 |
| Alternating areas of transmural inflammation and normal colon | Skip lesions (Crohn disease) | 392 |
| Site of diverticula | Sigmoid colon | 393 |
| Diverticulum in pharynx | Zenker diverticulum (diagnosed by barium swallow) | 394 |
| Hepatocellular carcinoma | HBV (+/– cirrhosis) or other causes of cirrhosis (eg, alcoholic liver disease, hemochromatosis), aflatoxins | 402 |
| Congenital conjugated hyperbilirubinemia (black liver) | Dubin-Johnson syndrome (inability of hepatocytes to secrete conjugated bilirubin into bile) | 404 |
| Hereditary harmless jaundice | Gilbert syndrome (benign congenital unconjugated hyperbilirubinemia) | 404 |
| Wilson disease | Hereditary *ATP7B* mutation (copper buildup in liver, brain, cornea, kidneys) | 405 |
| Hemochromatosis | Multiple blood transfusions or hereditary *HFE* mutation (can result in heart failure, "bronze diabetes," and ↑ risk of hepatocellular carcinoma) | 405 |
| Pancreatitis (acute) | Gallstones, alcohol | 407 |
| Pancreatitis (chronic) | Alcohol (adults), cystic fibrosis (kids) | 407 |
| Microcytic anemia | Iron deficiency | 428 |
| Autosplenectomy (fibrosis and shrinkage) | Sickle cell disease (hemoglobin S) | 432 |
| Bleeding disorder with GpIb deficiency | Bernard-Soulier syndrome (defect in platelet adhesion to von Willebrand factor) | 436 |
| Bleeding disorder with GpIIb/IIIa deficiency | Glanzmann thrombasthenia (defect in platelet-to-platelet aggregation) | 436 |
| Hereditary bleeding disorder | von Willebrand disease | 437 |
| Hereditary thrombophilia | Factor V Leiden | 437 |
| DIC | Severe sepsis, obstetric complications, cancer, burns, trauma, major surgery, acute pancreatitis, APL | 437 |
| Malignancy associated with noninfectious fever | Hodgkin lymphoma | 438 |
| Type of Hodgkin lymphoma | Nodular sclerosis | 438 |
| t(14;18) | Follicular lymphoma (*BCL-2* activation, anti-apoptotic oncogene) | 439, 444 |
| t(8;14) | Burkitt lymphoma (c-*myc* fusion, transcription factor oncogene) | 439, 444 |
| Type of non-Hodgkin lymphoma | Diffuse large B-cell lymphoma | 439 |
| 1° bone tumor (adults) | Multiple myeloma | 440 |
| Age ranges for patient with ALL/CLL/AML/CML | ALL: child, CLL: adult > 60, AML: adult ~ 65, CML: adult 45–85 | 442 |
| Malignancy (kids) | Leukemia, brain tumors | 442, 546 |

| DISEASE/FINDING | MOST COMMON/IMPORTANT ASSOCIATIONS | PAGE |
|---|---|---|
| Death in CML | Blast crisis | 442 |
| t(9;22) | Philadelphia chromosome, CML (*BCR-ABL* oncogene, tyrosine kinase activation), more rarely associated with ALL | 442, 444 |
| Vertebral compression fracture | Osteoporosis | 474 |
| HLA-B27 | Psoriatic arthritis, ankylosing spondylitis, IBD-associated arthritis, reactive arthritis | 481 |
| Death in SLE | Lupus nephropathy | 482 |
| Tumor of infancy | Strawberry hemangioma (grows rapidly and regresses spontaneously by childhood) | 492 |
| Actinic (solar) keratosis | Precursor to squamous cell carcinoma | 496 |
| Herald patch | Pityriasis rosea | 496 |
| Cerebellar tonsillar herniation | Chiari I malformation | 506 |
| Atrophy of the mammillary bodies | Wernicke encephalopathy (thiamine deficiency causing ataxia, ophthalmoplegia, and confusion) | 528 |
| Epidural hematoma | Rupture of middle meningeal artery (trauma; lentiform shaped) | 531 |
| Subdural hematoma | Rupture of bridging veins (crescent shaped) | 531 |
| Dementia | Alzheimer disease, multiple infarcts (vascular dementia) | 538, 539 |
| Demyelinating disease in young women | Multiple sclerosis | 541 |
| Brain tumor (adults) | Supratentorial: metastasis, astrocytoma (including glioblastoma multiforme), meningioma, schwannoma | 544 |
| Pituitary tumor | Prolactinoma, somatotropic adenoma | 545 |
| Brain tumor (children) | Infratentorial: medulloblastoma (cerebellum) or supratentorial: craniopharyngioma | 546 |
| Mixed (UMN and LMN) motor neuron disease | Amyotrophic lateral sclerosis | 548 |
| Degeneration of dorsal column fibers | Tabes dorsalis (3° syphilis), subacute combined degeneration (dorsal columns, lateral corticospinal, spinocerebellar tracts affected) | 548 |
| Glomerulonephritis (adults) | Berger disease (IgA nephropathy) | 620 |
| Nephrotic syndrome (adults) | Membranous nephropathy | 621 |
| Nephrotic syndrome (children) | Minimal change disease | 621 |
| Kidney stones | ▪ Calcium = radiopaque<br>▪ Struvite (ammonium) = radiopaque (formed by urease ⊕ organisms such as *Proteus mirabilis*, *S saprophyticus*, *Klebsiella*)<br>▪ Uric acid = radiolucent<br>▪ Cystine = faintly radiopaque | 622 |
| Renal tumor | Renal cell carcinoma: associated with von Hippel-Lindau and cigarette smoking; paraneoplastic syndromes (EPO, renin, PTHrP, ACTH) | 628 |
| 1° amenorrhea | Turner syndrome (45,XO or 45,XO/46,XX mosaic) | 661 |

| DISEASE/FINDING | MOST COMMON/IMPORTANT ASSOCIATIONS | PAGE |
|---|---|---|
| Neuron migration failure | Kallmann syndrome (hypogonadotropic hypogonadism and anosmia) | 662 |
| Clear cell adenocarcinoma of the vagina | DES exposure in utero | 668 |
| Ovarian tumor (benign, bilateral) | Serous cystadenoma | 670 |
| Ovarian tumor (malignant) | Serous carcinoma | 670 |
| Tumor in women | Leiomyoma (estrogen dependent, not precancerous) | 672 |
| Gynecologic malignancy | Endometrial carcinoma (most common in US); cervical carcinoma (most common worldwide) | 672 |
| Breast mass | Fibrocystic change, carcinoma (in postmenopausal women) | 673 |
| Breast tumor (benign, young woman) | Fibroadenoma | 673 |
| Breast cancer | Invasive ductal carcinoma | 674 |
| Testicular tumor | Seminoma (malignant, radiosensitive), ↑ placental ALP | 677 |
| Obstruction of male urinary tract | BPH | 678 |
| Hypercoagulability, endothelial damage, blood stasis | Virchow triad (↑ risk of thrombosis) | 695 |
| Pulmonary hypertension | Idiopathic, heritable, left heart disease (eg, HF), lung disease (eg, COPD), hypoxemic vasoconstriction (eg, OSA), thromboembolic (eg, PE) | 703 |
| SIADH | Small cell carcinoma of the lung | 709 |

## ▸ EQUATION REVIEW

| TOPIC | EQUATION | PAGE |
|---|---|---|
| Volume of distribution | $V_d = \dfrac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$ | 233 |
| Half-life | $t_{½} = \dfrac{0.7 \times V_d}{CL}$ | 233 |
| Drug clearance | $CL = \dfrac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e$ (elimination constant) | 233 |
| Loading dose | $LD = \dfrac{C_p \times V_d}{F}$ | 233 |
| Maintenance dose | $D = \dfrac{C_p \times CL \times \tau}{F}$ | 233 |
| Therapeutic index | TI = median toxic dose/median effective dose = $TD_{50}/ED_{50}$ | 237 |
| Odds ratio (for case-control studies) | $OR = \dfrac{a/c}{b/d} = \dfrac{ad}{bc}$ | 262 |
| Relative risk | $RR = \dfrac{a/(a + b)}{c/(c + d)}$ | 262 |

| TOPIC | EQUATION | PAGE |
|---|---|---|
| Attributable risk | $AR = \frac{a}{a+b} - \frac{c}{c+d}$ | 262 |
| Relative risk reduction | RRR = 1 – RR | 262 |
| Absolute risk reduction | $ARR = \frac{c}{c+d} - \frac{a}{a+b}$ | 262 |
| Number needed to treat | NNT = 1/ARR | 262 |
| Number needed to harm | NNH = 1/AR | 262 |
| Likelihood ratio + | LR+ = sensitivity/(1 – specificity) = TP rate/FP rate | 263 |
| Likelihood ratio – | LR– = (1 – sensitivity)/specificity = FN rate/TN rate | 263 |
| Sensitivity | Sensitivity = TP / (TP + FN) | 264 |
| Specificity | Specificity = TN / (TN + FP) | 264 |
| Positive predictive value | PPV = TP / (TP + FP) | 264 |
| Negative predictive value | NPV = TN / (FN + TN) | 264 |
| Cardiac output | $CO = \frac{\text{rate of } O_2 \text{ consumption}}{(\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content})}$<br>CO = stroke volume × heart rate | 294<br>294 |
| Mean arterial pressure | MAP = cardiac output × total peripheral resistance<br>MAP = ⅔ diastolic + ⅓ systolic | 294<br>294 |
| Stroke volume | SV = EDV – ESV | 294 |
| Ejection fraction | $EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$ | 294 |
| Resistance | $\text{Resistance} = \frac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$ | 295 |
| Capillary fluid exchange | $J_v$ = net fluid flow = $K_f[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$ | 305 |
| Reticulocyte production index | $RPI = \frac{\text{reticulocyte \% } \times \text{ actual Hct}}{\text{normal Hct } (\approx 45\%)}$ | 427 |
| Renal clearance | $C_x = (U_x V)/P_x$ | 606 |
| Glomerular filtration rate | $C_{inulin} = GFR = U_{inulin} \times V/P_{inulin}$<br>$= K_f [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$ | 606 |
| Effective renal plasma flow | $eRPF = U_{PAH} \times \frac{V}{P_{PAH}} = C_{PAH}$ | 606 |
| Renal blood flow | $RBF = \frac{RPF}{1 - Hct}$ | 606 |
| Filtration fraction | $FF = \frac{GFR}{RPF}$ | 607 |
| Henderson-Hasselbalch equation (for extracellular pH) | $pH = 6.1 + \log \frac{[HCO_3^-]}{0.03\ Pco_2}$ | 616 |
| Winters formula | $Pco_2 = 1.5\ [HCO_3^-] + 8 \pm 2$ | 616 |

| TOPIC | EQUATION | PAGE |
|---|---|---|
| Anion gap | $Na^+ - (Cl^- + HCO_3^-)$ | 616 |
| Physiologic dead space | $V_D = V_T \times \frac{Pa_{CO_2} - Pe_{CO_2}}{Pa_{CO_2}}$ | 688 |
| Pulmonary vascular resistance | $PVR = \frac{P_{pulm\ artery} - P_{L\ atrium}}{cardiac\ output}$ | 692 |
| Alveolar gas equation | $PA_{O_2} = PI_{O_2} - \frac{Pa_{CO_2}}{R}$ | 692 |

## ▶ EASILY CONFUSED MEDICATIONS

| DRUG | CLINICAL USE/MECHANISM OF ACTION |
|---|---|
| Amiloride | $K^+$-sparing diuretic |
| Amiodarone | Class III antiarrhythmic |
| Amlodipine | Dihydropyridine $Ca^{2+}$ channel blocker |
| Benztropine | Cholinergic antagonist |
| Bromocriptine | Dopamine agonist |
| Buspirone | Generalized anxiety disorder (5-$HT_{1A}$-receptor agonist) |
| Bupropion | Depression, smoking cessation (NE-DA reuptake inhibitor) |
| Cimetidine | $H_2$-receptor antagonist |
| Cetirizine | 2nd-generation antihistamine |
| Chloramphenicol | Antibiotic (blocks 50S subunit) |
| Chlordiazepoxide | Long-acting benzodiazepine |
| Chlorpromazine | Typical antipsychotic |
| Chlorpropamide | 1st-generation sulfonylurea |
| Chlorpheniramine | 1st-generation antihistamine |
| Chlorthalidone | Thiazide diuretic |
| Clozapine | Atypical antipsychotic |
| Clomipramine | Tricyclic antidepressant |
| Clomiphene | Selective estrogen receptor modulator |
| Clonidine | $\alpha_2$-agonist |
| Doxepin | Tricyclic antidepressant |
| Doxazosin | $\alpha_1$-antagonist |
| Eplerenone | $K^+$-sparing diuretic |
| Propafenone | Class IC antiarrhythmic |
| Fluoxetine | Selective serotonin reuptake inhibitor |
| Fluphenazine | Typical antipsychotic |
| Duloxetine | Serotonin-norepinephrine reuptake inhibitor |
| Mifepristone | Progesterone receptor antagonist |

| DRUG | CLINICAL USE/MECHANISM OF ACTION |
|---|---|
| Misoprostol | $PGE_1$ synthetic analog |
| Naloxone | Opioid receptor antagonist (treats toxicity) |
| Naltrexone | Opioid receptor antagonist (prevents relapse) |
| Nitroprusside | Hypertensive emergency (↑ cGMP/NO) |
| Nitroglycerin | Antianginal (↑ cGMP/NO) |
| Omeprazole | Proton pump inhibitor |
| Ketoconazole | Antifungal (inhibits fungal sterol synthesis) |
| Aripiprazole | Atypical antipsychotic |
| Anastrozole | Aromatase inhibitor |
| Rifaximin | Hepatic encephalopathy (↓ ammoniagenic bacteria) |
| Rifampin | Antimicrobial (inhibits DNA-dependent RNA polymerase) |
| Sertraline | Selective serotonin reuptake inhibitor |
| Selegiline | MAO-B inhibitor |
| Trazodone | Insomnia (blocks 5-$HT_2$, $\alpha_1$-adrenergic, and $H_1$ receptors) |
| Tramadol | Chronic pain (weak opioid agonist) |
| Varenicline | Smoking cessation (nicotinic ACh receptor partial agonist) |
| Venlafaxine | Serotonin-norepinephrine reuptake inhibitor |

## ▶ NOTES

SECTION IV

# Top-Rated Review Resources

*"Some books are to be tasted, others to be swallowed, and some few to be chewed and digested."*

—Sir Francis Bacon

*"Always read something that will make you look good if you die in the middle of it."*

—P.J. O'Rourke

*"So many books, so little time."*

—Frank Zappa

*"If one cannot enjoy reading a book over and over again, there is no use in reading it at all."*

—Oscar Wilde

*"Start where you are. Use what you have. Do what you can."*

—Arthur Ashe

## ▶ HOW TO USE THE DATABASE

This section is a database of top-rated basic science review books, sample examination books, websites, apps, and commercial review courses that have been marketed to medical students studying for the USMLE Step 1. For each recommended resource, we list (where applicable) the **Title**, the **First Author** (or editor), the **Series Name** (where applicable), the **Current Publisher**, the **Copyright Year**, the **Number of Pages**, the **ISBN**, the **Approximate List Price**, the **Format** of the resource, and the **Number of Test Questions**. We also include **Summary Comments** that describe their style and overall utility for studying. Finally, each recommended resource receives a **Rating**. Within each section, resources are arranged first by Rating and then alphabetically by the first author within each Rating group.

A letter rating scale with six different grades reflects the detailed student evaluations for **Rated Resources**. Each rated resource receives a rating as follows:

| | |
|---|---|
| A+ | Excellent for boards review. |
| A<br>A– | Very good for boards review; choose among the group. |
| B+<br>B | Good, but use only after exhausting better resources. |
| B– | Fair, but there are many better resources in the discipline; or low-yield subject material. |

The Rating is meant to reflect the overall usefulness of the resource in helping medical students prepare for the USMLE Step 1. This is based on a number of factors, including:

- The importance of the discipline for the USMLE Step 1
- The appropriateness and accuracy of the material
- The readability of the text
- The quality and number of sample questions
- The quality of written answers to sample questions
- The cost
- The quality of the user interface and learning experience, for web and mobile apps
- The quality and appropriateness of the images and illustrations
- The length of the text (longer is not necessarily better)
- The quality and number of other resources available in the same discipline

Please note that ratings do not reflect the quality of the resources for purposes other than reviewing for the USMLE Step 1. Many books with lower ratings are well written and informative but are not ideal for boards

preparation. We have not listed or commented on general textbooks available for the basic sciences.

Evaluations are based on the cumulative results of formal and informal surveys of thousands of medical students at many medical schools across the country. The summary comments and overall ratings represent a consensus opinion, but there may have been a broad range of opinion or limited student feedback on any particular resource.

Please note that the data listed are subject to change in that:

- Publisher and app store prices change frequently.
- Retail and online bookstores may set their own prices.
- New editions and app versions come out frequently, and the quality of updating varies.
- The same book may be reissued through another publisher.

We actively encourage medical students and faculty to submit their opinions and ratings of these basic science review materials so that we may update our database. In addition, we ask that publishers and authors submit for evaluation review copies of basic science review books, including new editions and books not included in our database. We also solicit reviews of new books, mobile apps, websites, flash cards, and commercial review courses.

### Disclaimer/Conflict of Interest Statement

None of the ratings reflects the opinion or influence of the publisher. All errors and omissions will gladly be corrected if brought to the attention of the authors through our blog at firstaidteam.com. Please note that USMLE-Rx, ScholarRx, and the entire *First Aid for the USMLE* series are publications by certain authors of *First Aid for the USMLE Step 1*; the following ratings are based solely on recommendations from the student authors of *First Aid for the USMLE Step 1* as well as data from the student survey and feedback forms.

# TOP-RATED REVIEW RESOURCES

## Question Banks

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| A+ | *UWorld Qbank* | UWorld | uworld.com | Test/3000+ q | \$269–\$799 |
| A | *NBME Practice Exams* | National Board of Medical Examiners | nbme.org/students/sas/Comprehensive.html | Test/200 q | \$60 |
| A− | *AMBOSS* | Amboss | amboss.com | Test/3500 q | \$59–\$286 |
| A− | *USMLE-Rx Qmax* | USMLE-Rx | usmle-rx.com | Test/2300+ q | \$79–\$349 |
| B+ | *Kaplan Qbank* | Kaplan | kaptest.com | Test/3300 q | \$99–\$599 |
| B+ | *TrueLearn Review* | | truelearn.com | Test/2200 q | \$160–\$400 |
| B | *BoardVitals* | | boardvitals.com | Test/3150 q | Free–\$189 |
| B | *Pastest* | | pastest.com | Test/2100 q | \$79–\$249 |

## Web and Mobile Apps

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| A | *Anki* | | ankisrs.net | Flash cards | Free |
| A | *Boards and Beyond* | | boardsbeyond.com | Review/Test/2300 q | \$19–\$299 |
| A | *SketchyMedical* | | sketchymedical.com | Review | \$100–\$550 |
| A | *Rx Bricks* | | usmle-rx.scholarrx.com/rx-bricks | Study plan | \$15–\$199 |
| A− | *Physeo* | | physeo.com | Review | \$30–\$150 |
| A− | *USMLE-Rx Step 1 Express* | | usmle-rx.com | Review/Test | \$49–\$199 |
| A− | *USMLE-Rx Step 1 Flash Facts* | | usmle-rx.com | Flash cards | \$29–\$149 |
| A− | *Dirty Medicine* | | youtube.com/c/DirtyMedicine | | Free |
| B+ | *USMLE Step 1 Mastery* | | builtbyhlt.com/medical/usmle-step-1-mastery | Test/1400 q | \$10–\$30 |
| B+ | *Cram Fighter* | | cramfighter.com | Study plan | \$29–\$159 |
| B+ | *Medical School Pathology* | | medicalschoolpathology.com | Review | Free |
| B+ | *OnlineMedEd* | | onlinemeded.org | Review | Free |
| B+ | *Osmosis* | | osmosis.org | Test | \$299–\$399 |
| B+ | *Medbullets* | | step1.medbullets.com | Review/Test/1000 q | Free–\$250 |
| B+ | *Ninja Nerd Medicine* | | youtube.com/c/NinjaNerdMedicine | | Free |
| B+ | *WebPath: The Internet Pathology Laboratory* | | webpath.med.utah.edu | Review/Test/1300 q | Free |
| B | *Digital Anatomist Project: Interactive Atlases* | | da.si.washington.edu/da.html | Review | Free |

| | | | | |
|---|---|---|---|---|
| B | *Dr. Najeeb Lectures* | drnajeeblectures.com | Review | $199 |
| B | *Firecracker* | firecracker.lww.com | Review/ Test/2800 q | $99–$499 |
| B | *KISSPrep* | kissprep.com | Review | $30–$150 |
| B | *Memorang* | memorangapp.com | Flash cards | $19–$239 |
| B | *Picmonic* | picmonic.com | Review | $25–$480 |
| B | *Radiopaedia.org* | radiopaedia.org | Cases/Test | Free |
| B⁻ | *Innerbody Research* | innerbody.com/htm/body.html | Review | Free |
| B⁻ | *Lecturio* | lecturio.com/usmle-step-1 | Review/ Test/2150 q | $105–$720 |

## Comprehensive

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| A | *First Aid for the Basic Sciences: General Principles* | Le | McGraw-Hill, 2017, 528 pages, ISBN 9781259587016 | Review | $75 |
| A | *First Aid Cases for the USMLE Step 1* | Le | McGraw-Hill, 2018, 496 pages, ISBN 9781260143133 | Cases | $50 |
| A⁻ | *First Aid for the Basic Sciences: Organ Systems* | Le | McGraw-Hill, 2017, 912 pages, ISBN 9781259587030 | Review | $72 |
| A⁻ | *Cracking the USMLE Step 1* | Princeton Review | Princeton Review, 2013, 832 pages, ISBN 9780307945068 | Review | $45 |
| B⁺ | *USMLE Step 1 Secrets in Color* | Brown | Elsevier, 2016, 800 pages, ISBN 9780323396790 | Review | $43 |
| B⁺ | *USMLE Step 1 Lecture Notes 2020* | Kaplan | Kaplan Medical, 2019, 2624 pages, ISBN 9781506254944 | Review | $330 |
| B⁺ | *Crush Step 1: The Ultimate USMLE Step 1 Review* | O'Connell | Elsevier, 2017, 704 pages, 9780323481632 | Review | $45 |
| B | *Kaplan USMLE Step 1 Qbook* | Kaplan | Kaplan Medical, 2017, 468 pages, ISBN 9781506223544 | Test/850 q | $50 |
| B | *medEssentials for the USMLE Step 1* | Kaplan | Kaplan Medical, 2019, 528 pages, ISBN 9781506223599 | Review | $55 |
| B | *Step-Up to USMLE Step 1 2015* | McInnis | Lippincott Williams & Wilkins, 2015, 528 pages, ISBN 9781469894690 | Review | $60 |
| B⁻ | *USMLE Step 1 Made Ridiculously Simple* | Carl | MedMaster, 2017, 416 pages, ISBN 9781935660224 | Review/Test 1000 q | $30 |

## Anatomy, Embryology, and Neuroscience

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| A⁻ | *High-Yield Gross Anatomy* | Dudek | Lippincott Williams & Wilkins, 2015, 320 pages, ISBN 9781451190236 | Review | $45 |
| A⁻ | *Clinical Anatomy Made Ridiculously Simple* | Goldberg | MedMaster, 2016, 175 pages, ISBN 9780940780972 | Review | $30 |

### Anatomy, Embryology, and Neuroscience *(continued)*

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| **B+** | ***BRS Embryology*** | Dudek | Lippincott Williams & Wilkins, 2014, 336 pages, ISBN 9781451190380 | Review/Test/220 q | $56 |
| **B+** | ***High-Yield Embryology*** | Dudek | Lippincott Williams & Wilkins, 2013, 176 pages, ISBN 9781451176100 | Review | $43 |
| **B+** | ***Clinical Neuroanatomy Made Ridiculously Simple*** | Goldberg | MedMaster, 2014, 99 pages, ISBN 9781935660194 | Review/Test/Few q | $26 |
| **B+** | ***High-Yield Neuroanatomy*** | Gould | Lippincott Williams & Wilkins, 2015, 208 pages, ISBN 9781451193435 | Review/Test/50 q | $42 |
| **B+** | ***Crash Course: Anatomy and Physiology*** | Stephens | Elsevier, 2019, 350 pages, ISBN 9780702073755 | Review | $40 |
| **B** | ***Anatomy—An Essential Textbook*** | Gilroy | Thieme, 2017, 528 pages, ISBN 9781626234390 | Text/Test/400 q | $50 |
| **B** | ***Netter's Anatomy Flash Cards*** | Hansen | Elsevier, 2018, 688 flash cards, ISBN 9780323530507 | Flash cards | $40 |
| **B** | ***Case Files: Anatomy*** | Toy | McGraw-Hill, 2014, 416 pages, ISBN 9780071794862 | Cases | $35 |
| **B−** | ***Case Files: Neuroscience*** | Toy | McGraw-Hill, 2014, 432 pages, ISBN 9780071790253 | Cases | $35 |

### Behavioral Science

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| **A−** | ***BRS Behavioral Science*** | Fadem | Lippincott Williams & Wilkins, 2020, 384 pages, ISBN 9781975118365 | Review/Test/600 q | $55 |
| **B** | ***Biostatistics and Epidemiology: A Primer for Health and Biomedical Professionals*** | Wassertheil-Smoller | Springer, 2015, 4th edition, 280 pages, 9781493921331 | Review | $75 |

### Biochemistry

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| **A−** | ***Pixorize*** | | pixorize.com | Review | $130–$200 |
| **B+** | ***Lippincott Illustrated Reviews: Biochemistry*** | Ferrier | Lippincott Williams & Wilkins, 2017, 560 pages, ISBN 9781496344496 | Review/Test/200 q | $78 |
| **B+** | ***BRS Biochemistry, Molecular Biology, and Genetics*** | Lieberman | Lippincott Williams & Wilkins, 2019, 448 pages, ISBN 9781496399236 | Review/Test/500 q | $55 |
| **B+** | ***PreTest Biochemistry and Genetics*** | Wilson | McGraw-Hill, 2013, 592 pages, ISBN 9780071791441 | Test/500 q | $38 |
| **B** | ***Lange Flash Cards Biochemistry and Genetics*** | Baron | McGraw-Hill, 2017, 184 flash cards, ISBN 9781259837210 | Flash cards | $40 |
| **B** | ***Case Files: Biochemistry*** | Toy | McGraw-Hill, 2014, 480 pages, ISBN 9780071794886 | Cases | $35 |

## Cell Biology and Histology

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| B+ | ***Blue Histology*** | | www.lab.anhb.uwa.edu.au/mb140 | Test | Free |
| B+ | ***Crash Course: Cell Biology and Genetics*** | Stubbs | Mosby, 2015, 216 pages, ISBN 9780723438762 | Review/Print + online | $47 |
| B | ***BRS Cell Biology and Histology*** | Gartner | Lippincott Williams & Wilkins, 2018, 448 pages, ISBN 9781496396358 | Review/ Test/320 q | $54 |

## Microbiology and Immunology

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| A− | ***Medical Microbiology and Immunology Flash Cards*** | Rosenthal | Elsevier, 2016, 192 flash cards, ISBN 9780323462242 | Flash cards | $40 |
| B+ | ***Basic Immunology*** | Abbas | Elsevier, 2019, 336 pages, ISBN 9780323549431 | Review | $70 |
| B+ | ***Clinical Microbiology Made Ridiculously Simple*** | Gladwin | MedMaster, 2019, 418 pages, ISBN 9781935660330 | Review | $38 |
| B+ | ***Microcards: Microbiology Flash Cards*** | Harpavat | Lippincott Williams & Wilkins, 2015, 312 flash cards, ISBN 9781451192353 | Flash cards | $53 |
| B+ | ***Review of Medical Microbiology and Immunology*** | Levinson | McGraw-Hill, 2020, 864 pages, ISBN 9781260116717 | Review/ Test/650 q | $77 |
| B+ | ***Lange Microbiology and Infectious Diseases Flash Cards, 3e*** | Somers | McGraw-Hill, 2017, ISBN 9781259859823 | Flash cards | $55 |
| B | ***Case Studies in Immunology: Clinical Companion*** | Geha | W. W. Norton & Company, 2016, 384 pages, ISBN 9780815345121 | Cases | $62 |
| B | ***How the Immune System Works*** | Sompayrac | Wiley-Blackwell, 2019, 168 pages, ISBN 9781119542124 | Review | $50 |
| B | ***Case Files: Microbiology*** | Toy | McGraw-Hill, 2014, 416 pages, ISBN 9780071820233 | Cases | $36 |
| B− | ***Lippincott Illustrated Reviews: Microbiology*** | Cornelissen | Lippincott Williams & Wilkins, 2019, 448 pages, ISBN 9781496395856 | Review/Test/ Few q | $74 |

## Pathology

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| A+ | ***Pathoma: Fundamentals of Pathology*** | Sattar | Pathoma, 2021, 226 pages, ISBN 9780983224648 | Review/ Lecture | $85–$120 |
| A− | ***Crash Course: Pathology*** | McKinney | Elsevier, 2019, 438 pages, ISBN 9780702073540 | Review | $40 |
| B+ | ***Rapid Review: Pathology*** | Goljan | Elsevier, 2018, 864 pages, ISBN 9780323476683 | Review/ Test/500 q | $65 |
| B+ | ***Robbins and Cotran Review of Pathology*** | Klatt | Elsevier, 2014, 504 pages, ISBN 9781455751556 | Test/1100 q | $55 |
| B | ***BRS Pathology*** | Gupta | Lippincott Williams & Wilkins, 2020, 496 pages, ISBN 9781975136628 | Review/ Test/450 q | $55 |
| B | ***Pathophysiology of Disease: Introduction to Clinical Medicine*** | Hammer | McGraw-Hill, 2018, 832 pages, ISBN 9781260026504 | Text | $90 |

## Pathology *(continued)*

| | | | | | |
|---|---|---|---|---|---|
| B | ***Haematology at a Glance*** | Mehta | Wiley-Blackwell, 2014, 136 pages, ISBN 9781119969228 | Review | $51 |
| B | ***Pocket Companion to Robbins and Cotran Pathologic Basis of Disease*** | Mitchell | Elsevier, 2016, 896 pages, ISBN 9781455754168 | Review | $39 |

## Pharmacology

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| B+ | ***Master the Boards USMLE Step 1 Pharmacology Flashcards*** | Fischer | Kaplan, 2015, 200 flash cards, ISBN 9781618657947 | Flash cards | $55 |
| B+ | ***Crash Course: Pharmacology*** | Page | Elsevier, 2019, 336 pages, ISBN 9780702073441 | Review | $40 |
| B+ | ***Katzung & Trevor's Pharmacology: Examination and Board Review*** | Trevor | McGraw-Hill, 2018, 592 pages, ISBN 9781259641022 | Review/ Test/800 q | $54 |
| B | ***Lange Pharmacology Flash Cards*** | Baron | McGraw-Hill, 2017, 266 flash cards, ISBN 9781259837241 | Flash cards | $39 |
| B | ***Pharmacology Flash Cards*** | Brenner | Elsevier, 2017, 230 flash cards, ISBN 9780323355643 | Flash cards | $45 |
| B | ***BRS Pharmacology*** | Lerchenfeldt | Lippincott Williams & Wilkins, 2019, 384 pages, ISBN 9781975105495 | Review/ Test/200 q | $55 |
| B− | ***Lippincott Illustrated Reviews: Pharmacology*** | Whalen | Lippincott Williams & Wilkins, 2018, 576 pages, ISBN 9781496384133 | Review/ Test/380 q | $76 |

## Physiology

| | | AUTHOR | PUBLISHER | TYPE | PRICE |
|---|---|---|---|---|---|
| A− | ***Physiology*** | Costanzo | Elsevier, 2017, 528 pages, ISBN 9780323478816 | Text | $60 |
| A− | ***Color Atlas of Physiology*** | Silbernagl | Thieme, 2015, 472 pages, ISBN 9783135450070 | Review | $50 |
| A− | ***Pulmonary Pathophysiology: The Essentials*** | West | Lippincott Williams & Wilkins, 2017, 264 pages, ISBN 9781496339447 | Review/ Test/75 q | $57 |
| B+ | ***BRS Physiology*** | Costanzo | Lippincott Williams & Wilkins, 2018, 304 pages, ISBN 9781496367617 | Review/ Test/350 q | $55 |
| B+ | ***Vander's Renal Physiology*** | Eaton | McGraw-Hill, 2018, 224 pages, ISBN 9781260019377 | Text | $49 |
| B+ | ***Pathophysiology of Heart Disease*** | Lilly | Lippincott Williams & Williams, 2020, 480 pages, ISBN 9781975120597 | Review | $57 |
| B+ | ***Acid-Base, Fluids, and Electrolytes Made Ridiculously Simple*** | Preston | MedMaster, 2017, 166 pages, ISBN 9781935660293 | Review | $24 |
| B | ***Endocrine Physiology*** | Molina | McGraw-Hill, 2018, 320 pages, ISBN 9781260019353 | Review | $59 |
| B | ***Netter's Physiology Flash Cards*** | Mulroney | Saunders, 2015, 450 flash cards, ISBN 9780323359542 | Flash cards | $40 |

SECTION IV

# Abbreviations and Symbols

| ABBREVIATION | MEANING |
|---|---|
| 1st MC* | 1st metacarpal |
| A-a | alveolar-arterial [gradient] |
| AA | Alcoholics Anonymous, amyloid A |
| AAMC | Association of American Medical Colleges |
| AAo* | ascending aorta |
| Ab | antibody |
| ABPA | allergic bronchopulmonary aspergillosis |
| AC | adenylyl cyclase |
| ACA | anterior cerebral artery |
| Acetyl-CoA | acetyl coenzyme A |
| ACD | anemia of chronic disease |
| ACE | angiotensin-converting enzyme |
| ACh | acetylcholine |
| AChE | acetylcholinesterase |
| ACL | anterior cruciate ligament |
| ACom | anterior communicating [artery] |
| ACTH | adrenocorticotropic hormone |
| AD | Alzheimer disease, autosomal dominant |
| ADA | adenosine deaminase, Americans with Disabilities Act |
| ADH | antidiuretic hormone |
| ADHD | attention-deficit hyperactivity disorder |
| ADP | adenosine diphosphate |
| ADPKD | autosomal-dominant polycystic kidney disease |
| AFP | α-fetoprotein |
| Ag | antigen, silver |
| AICA | anterior inferior cerebellar artery |
| AIDS | acquired immunodeficiency syndrome |
| AIHA | autoimmune hemolytic anemia |
| AKI | acute kidney injury |
| AKT | protein kinase B |
| AL | amyloid light [chain] |
| ALA | aminolevulinate |
| ALI | acute lung injury |
| ALL | acute lymphoblastic (lymphocytic) leukemia |
| ALP | alkaline phosphatase |
| ALS | amyotrophic lateral sclerosis |
| ALT | alanine transaminase |
| AMA | American Medical Association, antimitochondrial antibody |
| AML | acute myelogenous (myeloid) leukemia |
| AMP | adenosine monophosphate |
| ANA | antinuclear antibody |
| ANCA | antineutrophil cytoplasmic antibody |
| ANOVA | analysis of variance |

| ABBREVIATION | MEANING |
|---|---|
| ANP | atrial natriuretic peptide |
| ANS | autonomic nervous system |
| Ant* | anterior |
| anti-CCP | anti-cyclic citrullinated peptide |
| Ao* | aorta |
| AOA | American Osteopathic Association |
| AP | action potential, A & P [ribosomal binding sites] |
| APC | antigen-presenting cell, activated protein C |
| APL | Acute promyelocytic leukemia |
| Apo | apolipoprotein |
| APP | amyloid precursor protein |
| APRT | adenine phosphoribosyltransferase |
| aPTT | activated partial thromboplastin time |
| APUD | amine precursor uptake decarboxylase |
| AR | attributable risk, autosomal recessive, aortic regurgitation |
| ARB | angiotensin receptor blocker |
| ARDS | acute respiratory distress syndrome |
| Arg | arginine |
| ARPKD | autosomal-recessive polycystic kidney disease |
| ART | antiretroviral therapy |
| AS | aortic stenosis |
| ASA | anterior spinal artery |
| Asc* | ascending |
| Asc Ao* | ascending aorta |
| ASD | atrial septal defect |
| ASO | anti–streptolysin O |
| AST | aspartate transaminase |
| AT | angiotensin, antithrombin |
| ATN | acute tubular necrosis |
| ATP | adenosine triphosphate |
| ATPase | adenosine triphosphatase |
| ATTR | transthyretin-mediated amyloidosis |
| AUB | abnormal uterine bleeding |
| AV | atrioventricular |
| AZT | azidothymidine |
| BAL | British anti-Lewisite [dimercaprol] |
| BBB | blood-brain barrier |
| BCG | bacille Calmette-Guérin |
| BD* | bile duct |
| $BH_4$ | tetrahydrobiopterin |
| BM | basement membrane |
| BOOP | bronchiolitis obliterans organizing pneumonia |
| BP | bisphosphate, blood pressure |
| BPG | bisphosphoglycerate |

*Image abbreviation only

| ABBREVIATION | MEANING |
|---|---|
| BPH | benign prostatic hyperplasia |
| BT | bleeding time |
| BUN | blood urea nitrogen |
| C* | caudate |
| Ca* | capillary |
| $Ca^{2+}$ | calcium ion |
| CAD | coronary artery disease |
| CAF | common application form |
| cAMP | cyclic adenosine monophosphate |
| CBG | corticosteroid-binding globulin |
| Cbm* | cerebellum |
| CBSE | Comprehensive Basic Science Examination |
| CBSSA | Comprehensive Basic Science Self-Assessment |
| CBT | computer-based test, cognitive behavioral therapy |
| CC* | corpus callosum |
| CCA* | common carotid artery |
| CCK | cholecystokinin |
| CCS | computer-based case simulation |
| CD | cluster of differentiation |
| CDK | cyclin-dependent kinase |
| cDNA | complementary deoxyribonucleic acid |
| CEA | carcinoembryonic antigen |
| CETP | cholesteryl-ester transfer protein |
| CF | cystic fibrosis |
| CFTR | cystic fibrosis transmembrane conductance regulator |
| CGD | chronic granulomatous disease |
| cGMP | cyclic guanosine monophosphate |
| CGRP | calcitonin gene–related peptide |
| $C_H1$–$C_H3$ | constant regions, heavy chain [antibody] |
| ChAT | choline acetyltransferase |
| CHD* | common hepatic duct |
| $\chi^2$ | chi-squared |
| CI | confidence interval |
| CIN | candidate identification number, carcinoma in situ, cervical intraepithelial neoplasia |
| CIS | Communication and Interpersonal Skills |
| CK | clinical knowledge, creatine kinase |
| CKD | chronic kidney disease |
| CK-MB | creatine kinase, MB fraction |
| $C_L$ | constant region, light chain [antibody] |
| CL | clearance |
| $Cl^-$ | chloride ion |
| CLL | chronic lymphocytic leukemia |
| CMC | carpometacarpal (joint) |
| CML | chronic myelogenous (myeloid) leukemia |
| CMV | cytomegalovirus |
| CN | cranial nerve |
| $CN^-$ | cyanide ion |
| CNS | central nervous system |
| CNV | copy number variation |
| CO | carbon monoxide, cardiac output |
| $CO_2$ | carbon dioxide |
| CoA | coenzyme A |
| Coarct* | coarctation |

| ABBREVIATION | MEANING |
|---|---|
| COL1A1 | collagen, type I, alpha 1 |
| COL1A2 | collagen, type I, alpha 2 |
| COMT | catechol-O-methyltransferase |
| COP | coat protein |
| COPD | chronic obstructive pulmonary disease |
| CoQ | coenzyme Q |
| COVID-19 | Coronavirus disease 2019 |
| COX | cyclooxygenase |
| $C_p$ | plasma concentration |
| CPAP | continuous positive airway pressure |
| CPR | cardiopulmonary resuscitation |
| Cr | creatinine |
| CRC | colorectal cancer |
| CREST | calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerosis, and telangiectasias [syndrome] |
| CRH | corticotropin-releasing hormone |
| CRP | C-reactive protein |
| CS | clinical skills |
| C-section | cesarean section |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| CTP | cytidine triphosphate |
| CXR | chest x-ray |
| DA | dopamine |
| DAF | decay-accelerating factor |
| DAG | diacylglycerol |
| DAo* | descending aorta |
| dATP | deoxyadenosine triphosphate |
| DCIS | ductal carcinoma in situ |
| DCT | distal convoluted tubule |
| ddI | didanosine |
| DES | diethylstilbestrol |
| Desc Ao* | descending aorta |
| DHAP | dihydroxyacetone phosphate |
| DHEA | dehydroepiandrosterone |
| DHF | dihydrofolic acid |
| DHT | dihydrotestosterone |
| DI | diabetes insipidus |
| DIC | disseminated intravascular coagulation |
| DIP | distal interphalangeal [joint] |
| DKA | diabetic ketoacidosis |
| DLCO | diffusing capacity for carbon monoxide |
| DM | diabetes mellitus |
| DNA | deoxyribonucleic acid |
| DNR | do not resuscitate |
| dNTP | deoxynucleotide triphosphate |
| DO | doctor of osteopathy |
| DPGN | diffuse proliferative glomerulonephritis |
| DPM | doctor of podiatric medicine |
| DPP-4 | dipeptidyl peptidase-4 |
| DPPC | dipalmitoylphosphatidylcholine |
| DS | double stranded |
| dsDNA | double-stranded deoxyribonucleic acid |
| dsRNA | double-stranded ribonucleic acid |
| DRG | dorsal root ganglion |

*Image abbreviation only

| ABBREVIATION | MEANING |
|---|---|
| d4T | didehydrodeoxythymidine [stavudine] |
| dTMP | deoxythymidine monophosphate |
| DTR | deep tendon reflex |
| DTs | delirium tremens |
| dUDP | deoxyuridine diphosphate |
| dUMP | deoxyuridine monophosphate |
| DVT | deep venous thrombosis |
| E* | euthromatin, esophagus |
| EBV | Epstein-Barr virus |
| ECA* | external carotid artery |
| ECF | extracellular fluid |
| ECFMG | Educational Commission for Foreign Medical Graduates |
| ECG | electrocardiogram |
| ECL | enterochromaffin-like [cell] |
| ECM | extracellular matrix |
| ECT | electroconvulsive therapy |
| $ED_{50}$ | median effective dose |
| EDRF | endothelium-derived relaxing factor |
| EDTA | ethylenediamine tetra-acetic acid |
| EDV | end-diastolic volume |
| EEG | electroencephalogram |
| EF | ejection fraction |
| EGF | epidermal growth factor |
| EHEC | enterohemorrhagic *E coli* |
| EIEC | enteroinvasive *E coli* |
| ELISA | enzyme-linked immunosorbent assay |
| EM | electron micrograph/microscopy |
| EMB | eosin–methylene blue |
| EPEC | eneteropathogenic *E coli* |
| Epi | epinephrine |
| EPO | erythropoietin |
| EPS | extrapyramidal system |
| ER | endoplasmic reticulum, estrogen receptor |
| ERAS | Electronic Residency Application Service |
| ERCP | endoscopic retrograde cholangiopancreatography |
| ERP | effective refractory period |
| eRPF | effective renal plasma flow |
| ERT | estrogen replacement therapy |
| ERV | expiratory reserve volume |
| ESR | erythrocyte sedimentation rate |
| ESRD | end-stage renal disease |
| ESV | end-systolic volume |
| ETEC | enterotoxigenic *E coli* |
| EtOH | ethyl alcohol |
| EV | esophageal vein |
| F | bioavailability |
| FA | fatty acid |
| Fab | fragment, antigen-binding |
| FAD | flavin adenine dinucleotide |
| $FADH_2$ | reduced flavin adenine dinucleotide |
| FAP | familial adenomatous polyposis |
| F1,6BP | fructose-1,6-bisphosphate |
| F2,6BP | fructose-2,6-bisphosphate |
| FBPase | fructose bisphosphatase |

| ABBREVIATION | MEANING |
|---|---|
| FBPase-2 | fructose bisphosphatase-2 |
| Fc | fragment, crystallizable |
| FcR | Fc receptor |
| 5f-dUMP | 5-fluorodeoxyuridine monophosphate |
| $Fe^{2+}$ | ferrous ion |
| $Fe^{3+}$ | ferric ion |
| Fem* | femur |
| FENa | excreted fraction of filtered sodium |
| $FEV_1$ | forced expiratory volume in 1 second |
| FF | filtration fraction |
| FFA | free fatty acid |
| FGF | fibroblast growth factor |
| FGFR | fibroblast growth factor receptor |
| FISH | fluorescence in situ hybridization |
| FIT | fecal immunochemical testing |
| FKBP | FK506 binding protein |
| fMet | formylmethionine |
| FMG | foreign medical graduate |
| FMN | flavin mononucleotide |
| FN | false negative |
| FP, FP* | false positive, foot process |
| FRC | functional residual capacity |
| FSH | follicle-stimulating hormone |
| FSMB | Federation of State Medical Boards |
| FTA-ABS | fluorescent treponemal antibody—absorbed |
| FTD* | frontotemporal dementia |
| 5-FU | 5-fluorouracil |
| FVC | forced vital capacity |
| GABA | γ-aminobutyric acid |
| GAG | glycosaminoglycan |
| Gal | galactose |
| GBM | glomerular basement membrane |
| GC | glomerular capillary |
| G-CSF | granulocyte colony-stimulating factor |
| GERD | gastroesophageal reflux disease |
| GFAP | glial fibrillary acid protein |
| GFR | glomerular filtration rate |
| GGT | γ-glutamyl transpeptidase |
| GH | growth hormone |
| GHB | γ-hydroxybutyrate |
| GHRH | growth hormone–releasing hormone |
| $G_I$ | G protein, I polypeptide |
| GI | gastrointestinal |
| GIP | gastric inhibitory peptide |
| GIST | gastrointestinal stromal tumor |
| GLUT | glucose transporter |
| GM | granulocyte macrophage |
| GM-CSF | granulocyte-macrophage colony stimulating factor |
| GMP | guanosine monophosphate |
| GnRH | gonadotropin-releasing hormone |
| Gp | glycoprotein |
| G6P | glucose-6-phosphate |
| G6PD | glucose-6-phosphate dehydrogenase |
| GPe | globus pallidus externa |

*Image abbreviation only

| ABBREVIATION | MEANING |
|---|---|
| GPi | globus pallidus interna |
| GPI | glycosyl phosphatidylinositol |
| GRP | gastrin-releasing peptide |
| $G_S$ | G protein, S polypeptide |
| GSH | reduced glutathione |
| GSSG | oxidized glutathione |
| GTP | guanosine triphosphate |
| GTPase | guanosine triphosphatase |
| GU | genitourinary |
| H* | heterochromatin |
| $H^+$ | hydrogen ion |
| $H_1$, $H_2$ | histamine receptors |
| $H_2S$ | hydrogen sulfide |
| HA* | hepatic artery |
| HAV | hepatitis A virus |
| HAVAb | hepatitis A antibody |
| Hb | hemoglobin |
| HBcAb/HBcAg | hepatitis B core antibody/antigen |
| HBeAb/HBeAg | hepatitis B early antibody/antigen |
| HBsAb/HBsAg | hepatitis B surface antibody/antigen |
| $HbCO_2$ | carbaminohemoglobin |
| HBV | hepatitis B virus |
| HCC | hepatocellular carcinoma |
| hCG | human chorionic gonadotropin |
| $HCO_3^-$ | bicarbonate |
| Hct | hematocrit |
| HCTZ | hydrochlorothiazide |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HDN | hemolytic disease of the newborn |
| HDV | hepatitis D virus |
| H&E | hematoxylin and eosin |
| HEV | hepatitis E virus |
| HF | heart failure |
| Hfr | high-frequency recombination [cell] |
| HFpEF | heart failure with preserved ejection fraction |
| HFrEF | heart failure with reduced ejection fraction |
| HGPRT | hypoxanthine-guanine phosphoribosyltransferase |
| HHb | deoxygenated hemoglobin |
| HHS | hyperosmolar hyperglycemic state |
| HHV | human herpesvirus |
| 5-HIAA | 5-hydroxyindoleacetic acid |
| HIT | heparin-induced thrombocytopenia |
| HIV | human immunodeficiency virus |
| HL | hepatic lipase |
| HLA | human leukocyte antigen |
| HMG-CoA | hydroxymethylglutaryl-coenzyme A |
| HMP | hexose monophosphate |
| HMWK | high-molecular-weight kininogen |
| HNPCC | hereditary nonpolyposis colorectal cancer |
| hnRNA | heterogeneous nuclear ribonucleic acid |
| $H_2O_2$ | hydrogen peroxide |
| HOCM | hypertrophic obstructive cardiomyopathy |
| HPA | hypothalamic-pituitary-adrenal [axis] |

*Image abbreviation only

| ABBREVIATION | MEANING |
|---|---|
| HPO | hypothalamic-pituitary-ovarian [axis] |
| HPV | human papillomavirus |
| HR | heart rate |
| HSP | Henoch-Schönlein purpura |
| HSV | herpes simplex virus |
| 5-HT | 5-hydroxytryptamine (serotonin) |
| HTLV | human T-cell leukemia virus |
| HTN | hypertension |
| HUS | hemolytic-uremic syndrome |
| HVA | homovanillic acid |
| IBD | inflammatory bowel disease |
| IBS | irritable bowel syndrome |
| IC | inspiratory capacity, immune complex |
| $I_{Ca}$ | calcium current [heart] |
| $I_f$ | funny current [heart] |
| ICA | internal carotid artery |
| ICAM | intercellular adhesion molecule |
| ICD | implantable cardioverter defibrillator |
| ICE | Integrated Clinical Encounter |
| ICF | intracellular fluid |
| ICP | intracranial pressure |
| ID | identification |
| $ID_{50}$ | median infective dose |
| IDL | intermediate-density lipoprotein |
| IF | immunofluorescence, initiation factor |
| IFN | interferon |
| Ig | immunoglobulin |
| IGF | insulin-like growth factor |
| $I_K$ | potassium current [heart] |
| IL | interleukin |
| IM | intramuscular |
| IMA | inferior mesenteric artery |
| IMG | international medical graduate |
| IMP | inosine monophosphate |
| IMV | inferior mesenteric vein |
| $I_{Na}$ | sodium current [heart] |
| INH | isoniazid |
| INO | internuclear ophthalmoplegia |
| INR | International Normalized Ratio |
| IO | inferior oblique [muscle] |
| IOP | intraocular pressure |
| $IP_3$ | inositol triphosphate |
| IPV | inactivated polio vaccine |
| IR | current × resistance [Ohm's law], inferior rectus [muscle] |
| IRV | inspiratory reserve volume |
| ITP | idiopathic thrombocytopenic purpura |
| IUD | intrauterine device |
| IUGR | intrauterine growth restriction |
| IV | intravenous |
| IVC | inferior vena cava |
| IVDU | intravenous drug use |
| IVIG | intravenous immunoglobulin |
| JAK/STAT | Janus kinase/signal transducer and activator of transcription [pathway] |

| ABBREVIATION | MEANING |
|---|---|
| JGA | juxtaglomerular apparatus |
| JVD | jugular venous distention |
| JVP | jugular venous pulse |
| $K^+$ | potassium ion |
| KatG | catalase-peroxidase produced by *M tuberculosis* |
| $K_e$ | elimination constant |
| $K_f$ | filtration constant |
| KG | ketoglutarate |
| Kid* | kidney |
| $K_m$ | Michaelis-Menten constant |
| KOH | potassium hydroxide |
| L | left, lentiform, liver |
| LA | left atrial, left atrium |
| LAD | left anterior descending coronary artery |
| LAP | leukocyte alkaline phosphatase |
| Lat cond* | lateral condyle |
| Lb* | lamellar body |
| LCA | left coronary artery |
| LCAT | lecithin-cholesterol acyltransferase |
| LCC* | left common carotid artery |
| LCFA | long-chain fatty acid |
| LCL | lateral collateral ligament |
| LCME | Liaison Committee on Medical Education |
| LCMV | lymphocytic choriomeningitis virus |
| LCX | left circumflex coronary artery |
| LD | loading dose |
| $LD_{50}$ | median lethal dose |
| LDH | lactate dehydrogenase |
| LDL | low-density lipoprotein |
| LES | lower esophageal sphincter |
| LFA | leukocyte function–associated antigen |
| LFT | liver function test |
| LH | luteinizing hormone |
| Liv* | liver |
| LLL* | left lower lobe (of lung) |
| LLQ | left lower quadrant |
| LM | lateral meniscus, left main coronary artery, light microscopy |
| LMN | lower motor neuron |
| LOS | lipooligosaccharide |
| LPA* | left pulmonary artery |
| LPL | lipoprotein lipase |
| LPS | lipopolysaccharide |
| LR | lateral rectus [muscle] |
| LT | labile toxin, leukotriene |
| LUL* | left upper lobe (of lung) |
| LV | left ventricle, left ventricular |
| $M_1$-$M_5$ | muscarinic (parasympathetic) ACh receptors |
| MAC | membrane attack complex, minimum alveolar concentration |
| MALT | mucosa-associated lymphoid tissue |
| MAO | monoamine oxidase |
| MAOI | monoamine oxidase inhibitor |
| MAP | mean arterial pressure, mitogen-activated protein |
| Max* | maxillary sinus |

| ABBREVIATION | MEANING |
|---|---|
| MC | midsystolic click, metacarpal |
| MCA | middle cerebral artery |
| MCAT | Medical College Admissions Test |
| MCHC | mean corpuscular hemoglobin concentration |
| MCL | medial collateral ligament |
| MCP | metacarpophalangeal [joint] |
| MCV | mean corpuscular volume |
| MD | maintenance dose |
| MDD | major depressive disorder |
| Med cond* | medial condyle |
| MELAS syndrome | mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes |
| MEN | multiple endocrine neoplasia |
| MERS | Middle East respiratory syndrome |
| $Mg^{2+}$ | magnesium ion |
| $MgSO_4$ | magnesium sulfate |
| MHC | major histocompatibility complex |
| MI | myocardial infarction |
| MIF | müllerian inhibiting factor |
| MIRL | membrane inhibitor of reactive lysis |
| MLCK | myosin light-chain kinase |
| MLF | medial longitudinal fasciculus |
| MMC | migrating motor complex |
| MMR | measles, mumps, rubella [vaccine] |
| MODY | maturity onset diabetes of the young |
| 6-MP | 6-mercaptopurine |
| MPGN | membranoproliferative glomerulonephritis |
| MPO | myeloperoxidase |
| MPO-ANCA/ p-ANCA | myeloperoxidase/perinuclear antineutrophil cytoplasmic antibody |
| MR | medial rectus [muscle], mitral regurgitation |
| MRI | magnetic resonance imaging |
| miRNA | microribonucleic acid |
| mRNA | messenger ribonucleic acid |
| MRSA | methicillin-resistant *S aureus* |
| MS | mitral stenosis, multiple sclerosis |
| MSH | melanocyte-stimulating hormone |
| mtDNA | mitochondrial DNA |
| mTOR | mammalian target of rapamycin |
| MTP | metatarsophalangeal [joint] |
| MTX | methotrexate |
| $MVO_2$ | myocardial oxygen consumption |
| MVP | mitral valve prolapse |
| N* | nucleus |
| $Na^+$ | sodium ion |
| NAT | nucleic acid testing |
| NAD | nicotinamide adenine dinucleotide |
| $NAD^+$ | oxidized nicotinamide adenine dinucleotide |
| NADH | reduced nicotinamide adenine dinucleotide |
| $NADP^+$ | oxidized nicotinamide adenine dinucleotide phosphate |
| NADPH | reduced nicotinamide adenine dinucleotide phosphate |
| NBME | National Board of Medical Examiners |
| NBOME | National Board of Osteopathic Medical Examiners |
| NBPME | National Board of Podiatric Medical Examiners |

*Image abbreviation only

| ABBREVIATION | MEANING |
|---|---|
| NE | norepinephrine |
| NF | neurofibromatosis |
| NFAT | nuclear factor of activated T-cell |
| $NH_3$ | ammonia |
| $NH_4^+$ | ammonium |
| NK | natural killer [cells] |
| $N_M$ | muscarinic ACh receptor in neuromuscular junction |
| NMDA | *N*-methyl-d-aspartate |
| NMJ | neuromuscular junction |
| NMS | neuroleptic malignant syndrome |
| $N_N$ | nicotinic ACh receptor in autonomic ganglia |
| NRMP | National Residency Matching Program |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NO | nitric oxide |
| $N_2O$ | nitrous oxide |
| NPH | neutral protamine Hagedorn, normal pressure hydrocephalus |
| NPV | negative predictive value |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NSAID | nonsteroidal anti-inflammatory drug |
| NSE | neuron-specific enolase |
| NSTEMI | non–ST-segment elevation myocardial infarction |
| Nu* | nucleolus |
| OAA | oxaloacetic acid |
| OCD | obsessive-compulsive disorder |
| OCP | oral contraceptive pill |
| ODC | oxygen-hemoglobin dissociation curve |
| OH | hydroxy |
| 1,25-OH $D_3$ | calcitriol (active form of vitamin D) |
| 25-OH $D_3$ | storage form of vitamin D |
| OPV | oral polio vaccine |
| OR | odds ratio |
| OS | opening snap |
| OSA | obstructive sleep apnea |
| OVLT | organum vasculosum of the lamina terminalis |
| P-body | processing body (cytoplasmic) |
| P-450 | cytochrome P-450 family of enzymes |
| PA | posteroanterior, pulmonary artery |
| PABA | *para*-aminobenzoic acid |
| $Pa_{CO_2}$ | arterial $P_{CO_2}$ |
| $P_{ACO_2}$ | alveolar $P_{CO_2}$ |
| PAH | *para*-aminohippuric acid |
| PAN | polyarteritis nodosa |
| $Pa_{O_2}$ | partial pressure of oxygen in arterial blood |
| $P_{AO_2}$ | partial pressure of oxygen in alveolar blood |
| PAP | Papanicolaou [smear], prostatic acid phosphatase, posteromedial papillary muscle |
| PAPPA | pregnancy-associated plasma protein A |
| PAS | periodic acid–Schiff |
| Pat* | patella |
| PBP | penicillin-binding protein |
| PC | platelet count, pyruvate carboxylase |
| PCA | posterior cerebral artery |
| PCC | prothrombin complex concentrate |
| PCL | posterior cruciate ligament |
| $P_{CO_2}$ | partial pressure of carbon dioxide |
| PCom | posterior communicating [artery] |
| PCOS | polycystic ovarian syndrome |
| PCP | phencyclidine hydrochloride, *Pneumocystis jirovecii* pneumonia |
| PCR | polymerase chain reaction |
| PCT | proximal convoluted tubule |
| PCV13 | pneumococcal conjugate vaccine |
| PCWP | pulmonary capillary wedge pressure |
| PDA | patent ductus arteriosus, posterior descending artery |
| PDE | phosphodiesterase |
| PDGF | platelet-derived growth factor |
| PDH | pyruvate dehydrogenase |
| PE | pulmonary embolism |
| PECAM | platelet–endothelial cell adhesion molecule |
| $P_{ECO_2}$ | expired air $P_{CO_2}$ |
| PEP | phosphoenolpyruvate |
| PF | platelet factor |
| PFK | phosphofructokinase |
| PFK-2 | phosphofructokinase-2 |
| PFT | pulmonary function test |
| PG | phosphoglycerate |
| $P_i$ | plasma interstitial osmotic pressure, inorganic phosphate |
| PICA | posterior inferior cerebellar artery |
| PID | pelvic inflammatory disease |
| $P_{IO_2}$ | $P_{O_2}$ in inspired air |
| PIP | proximal interphalangeal [joint] |
| $PIP_2$ | phosphatidylinositol 4,5-bisphosphate |
| $PIP_3$ | phosphatidylinositol 3,4,5-bisphosphate |
| PKD | polycystic kidney disease |
| PKR | interferon-α–induced protein kinase |
| PKU | phenylketonuria |
| PLP | pyridoxal phosphate |
| PML | progressive multifocal leukoencephalopathy |
| PMN | polymorphonuclear [leukocyte] |
| $P_{net}$ | net filtration pressure |
| PNET | primitive neuroectodermal tumor |
| PNS | peripheral nervous system |
| $P_{O_2}$ | partial pressure of oxygen |
| $PO_4^{3-}$ | phosphate |
| Pop* | popliteal artery |
| Pop a* | popliteal artery |
| Post* | posterior |
| PPAR | peroxisome proliferator-activated receptor |
| PPD | purified protein derivative |
| PPI | proton pump inhibitor |
| PPM | parts per million |
| PPSV23 | pneumococcal polysaccharide vaccine |
| PPV | positive predictive value |
| PR3-ANCA/ c-ANCA | cytoplasmic antineutrophil cytoplasmic antibody |
| PrP | prion protein |
| PRPP | phosphoribosylpyrophosphate |

*Image abbreviation only

| ABBREVIATION | MEANING |
|---|---|
| PSA | prostate-specific antigen |
| PSS | progressive systemic sclerosis |
| PT | prothrombin time |
| *PTEN* | phosphatase and tensin homolog |
| PTH | parathyroid hormone |
| PTHrP | parathyroid hormone–related protein |
| PTSD | post-traumatic stress disorder |
| PTT | partial thromboplastin time |
| PV | plasma volume, venous pressure, portal vein |
| Pv* | pulmonary vein |
| PVC | polyvinyl chloride |
| PVR | pulmonary vascular resistance |
| R | correlation coefficient, right, R variable [group] |
| $R_3$ | Registration, Ranking, & Results [system] |
| RA | right atrium |
| RAAS | renin-angiotensin-aldosterone system |
| RANK-L | receptor activator of nuclear factor-κ B ligand |
| RAS | reticular activating system |
| RBF | renal blood flow |
| RCA | right coronary artery |
| REM | rapid eye movement |
| RER | rough endoplasmic reticulum |
| Rh | *rhesus* antigen |
| RLL* | right lower lobe (of lungs) |
| RLQ | right lower quadrant |
| RML* | right middle lobe (of lung) |
| RNA | ribonucleic acid |
| RNP | ribonucleoprotein |
| ROS | reactive oxygen species |
| RPF | renal plasma flow |
| RPGN | rapidly progressive glomerulonephritis |
| RPR | rapid plasma reagin |
| RR | relative risk, respiratory rate |
| rRNA | ribosomal ribonucleic acid |
| RS | Reed-Sternberg [cells] |
| RSC* | right subclavian artery |
| RSV | respiratory syncytial virus |
| RTA | renal tubular acidosis |
| RUL* | right upper lobe (of lung) |
| RUQ | right upper quadrant |
| RV | residual volume, right ventricle, right ventricular |
| RVH | right ventricular hypertrophy |
| [S] | substrate concentration |
| SA | sinoatrial |
| SAA | serum amyloid–associated [protein] |
| SAM | S-adenosylmethionine |
| SARS | severe acute respiratory syndrome |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 (virus) |
| SCC | squamous cell carcinoma |
| SCD | sudden cardiac death |
| SCID | severe combined immunodeficiency disease |
| SCJ | squamocolumnar junction |
| SCM | sternocleidomastoid muscle |
| SCN | suprachiasmatic nucleus |

*Image abbreviation only

| ABBREVIATION | MEANING |
|---|---|
| SD | standard deviation |
| SE | standard error [of the mean] |
| SEP | Spoken English Proficiency |
| SER | smooth endoplasmic reticulum |
| SERM | selective estrogen receptor modulator |
| SGLT | sodium-glucose transporter |
| SHBG | sex hormone–binding globulin |
| SIADH | syndrome of inappropriate [secretion of] antidiuretic hormone |
| SIDS | sudden infant death syndrome |
| SJS | Stevens-Johnson syndrome |
| SLE | systemic lupus erythematosus |
| SLL | small lymphocytic lymphoma |
| SLT | Shiga-like toxin |
| SMA | superior mesenteric artery |
| SMX | sulfamethoxazole |
| SNARE | soluble NSF attachment protein receptor |
| SNc | substantia nigra pars compacta |
| SNP | single nucleotide polymorphism |
| SNr | substantia nigra pars reticulata |
| SNRI | serotonin and norepinephrine receptor inhibitor |
| snRNA | small nuclear RNA |
| snRNP | small nuclear ribonucleoprotein |
| SO | superior oblique [muscle] |
| SOAP | Supplemental Offer and Acceptance Program |
| Sp* | spleen |
| spp | species |
| SR | superior rectus [muscle] |
| SS | single stranded |
| ssDNA | single-stranded deoxyribonucleic acid |
| SSPE | subacute sclerosing panencephalitis |
| SSRI | selective serotonin reuptake inhibitor |
| ssRNA | single-stranded ribonucleic acid |
| St* | stomach |
| ST | Shiga toxin |
| StAR | steroidogenic acute regulatory protein |
| STEMI | ST-segment elevation myocardial infarction |
| STI | sexually transmitted infection |
| STN | subthalamic nucleus |
| SV | splenic vein, stroke volume |
| SVC | superior vena cava |
| SVR | systemic vascular resistance |
| SVT | supraventricular tachycardia |
| T* | thalamus, trachea |
| $t_{1/2}$ | half-life |
| $T_3$ | triiodothyronine |
| $T_4$ | thyroxine |
| TAPVR | total anomalous pulmonary venous return |
| TB | tuberculosis |
| TBG | thyroxine-binding globulin |
| TBV | total blood volume |
| 3TC | dideoxythiacytidine [lamivudine] |
| TCA | tricarboxylic acid [cycle], tricyclic antidepressant |
| Tc cell | cytotoxic T cell |
| TCR | T-cell receptor |

| ABBREVIATION | MEANING |
|---|---|
| TDF | tenofovir disoproxil fumarate |
| TdT | terminal deoxynucleotidyl transferase |
| TE | tracheoesophageal |
| TFT | thyroid function test |
| TG | triglyceride |
| TGF | transforming growth factor |
| Th cell | helper T cell |
| THF | tetrahydrofolic acid |
| TI | therapeutic index |
| TIA | transient ischemic attack |
| Tib* | tibia |
| TIBC | total iron-binding capacity |
| TIPS | transjugular intrahepatic portosystemic shunt |
| TLC | total lung capacity |
| $T_m$ | maximum rate of transport |
| TMP | trimethoprim |
| TN | true negative |
| TNF | tumor necrosis factor |
| TNM | tumor, node, metastases [staging] |
| TOP | topoisomerase |
| ToRCHeS | *Toxoplasma gondii*, rubella, CMV, HIV, HSV-2, syphilis |
| TP | true positive |
| tPA | tissue plasminogen activator |
| TPO | thyroid peroxidase, thrombopoietin |
| TPP | thiamine pyrophosphate |
| TPPA | *Treponema pallidum* particle agglutination assay |
| TPR | total peripheral resistance |
| TR | tricuspid regurgitation |
| TRAP | tartrate-resistant acid phosphatase |
| TRECs | T-cell receptor excision circles |
| TRH | thyrotropin-releasing hormone |
| tRNA | transfer ribonucleic acid |
| TSH | thyroid-stimulating hormone |
| TSI | triple sugar iron |
| TSS | toxic shock syndrome |
| TSST | toxic shock syndrome toxin |
| TTP | thrombotic thrombocytopenic purpura |
| TTR | transthyretin |
| TV | tidal volume |
| $TXA_2$ | thromboxane $A_2$ |
| UDP | uridine diphosphate |

*Image abbreviation only

| ABBREVIATION | MEANING |
|---|---|
| UMN | upper motor neuron |
| UMP | uridine monophosphate |
| UPD | uniparental disomy |
| URI | upper respiratory infection |
| USMLE | United States Medical Licensing Examination |
| UTI | urinary tract infection |
| UTP | uridine triphosphate |
| UV | ultraviolet |
| $V_1$, $V_2$ | vasopressin receptors |
| VC | vital capacity |
| $V_d$ | volume of distribution |
| VD | physiologic dead space |
| V(D)J | variable, (diversity), joining gene segments rearranged to form Ig genes |
| VDRL | Venereal Disease Research Laboratory |
| VEGF | vascular endothelial growth factor |
| $V_H$ | variable region, heavy chain [antibody] |
| VHL | von Hippel-Lindau [disease] |
| VIP | vasoactive intestinal peptide |
| VIPoma | vasoactive intestinal polypeptide-secreting tumor |
| VJ | light-chain hypervariable region [antibody] |
| $V_L$ | variable region, light chain [antibody] |
| VLCFA | very-long-chain fatty acids |
| VLDL | very low density lipoprotein |
| VMA | vanillylmandelic acid |
| VMAT | vesicular monoamine transporter |
| $V_{max}$ | maximum velocity |
| VPL | ventral posterior nucleus, lateral |
| VPM | ventral posterior nucleus, medial |
| VPN | vancomycin, polymyxin, nystatin [media] |
| $\dot{V}/\dot{Q}$ | ventilation/perfusion [ratio] |
| VRE | vancomycin-resistant enterococcus |
| VSD | ventricular septal defect |
| $V_T$ | tidal volume |
| VTE | venous thromboembolism |
| vWF | von Willebrand factor |
| VZV | varicella-zoster virus |
| VMAT | vesicular monoamine transporter |
| XR | X-linked recessive |
| XX/XY | normal complement of sex chromosomes for female/male |
| ZDV | zidovudine [formerly AZT] |

SECTION IV

# Image Acknowledgments

In this edition, in collaboration with MedIQ Learning, LLC, and a variety of other partners, we are pleased to include the following clinical images and diagrams for the benefit of integrative student learning.

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## Biochemistry

34 **Chromatin structure.** Electron micrograph showing heterochromatin, euchromatin, and nucleolus. This image is a derivative work, adapted from the following source, available under : Roller RA, Rickett JD, Stickle WB. The hypobranchial gland of the estuarine snail *Stramonita haemastoma canaliculata* (Gray) (Prosobranchia: Muricidae): a light and electron microscopical study. *Am Malac Bull.* 1995;11(2):177-190. Available at https://archive.org/details/americanm101119931994amer.

49 **Cilia structure: Image A.** Nine doublet + 2 singlet arrangement of microtubule. Courtesy of Louisa Howard and Michael Binder. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

49 **Cilia structure: Image B.** Cilia structure of basal body. This image is a derivative work, adapted from the following source, available under : Riparbelli MG, Cabrera OA, Callaini G, et al. Unique properties of *Drosophila* spermatocyte primary cilia. *Biol Open.* 2013 Nov 15; 2(11): 1137–1147. DOI: 10.1242/bio.20135355.

49 **Cilia structure: Image C.** Dextrocardia. This image is a derivative work, adapted from the following source, available under : Oluwadare O, Ayoka AO, Akomolafe RO, et al. The role of electrocardiogram in the diagnosis of dextrocardia with mirror image atrial arrangement and ventricular position in a young adult Nigerian in Ile-Ife: a case report. *J Med Case Rep.* 2015;9:222. DOI: 10.1186/s13256-015-0695-4.

51 **Osteogenesis imperfecta: Image A.** Skeletal deformities in upper extremity of child. This image is a derivative work, adapted from the following source, available under : Vanakker OM, Hemelsoet D, De Paepe. Hereditary connective tissue diseases in young adult stroke: a comprehensive synthesis. *Stroke Res Treat.* 2011;712903. DOI: 10.4061/2011/712903. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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55 **Karyotyping.** Paar C, Herber G, Voskova, et al. This image is a derivative work, adapted from the following source, available under : A case of acute myeloid leukemia (AML) with an unreported combination of chromosomal abnormalities: gain of isochromosome 5p, tetrasomy 8 and unbalanced translocation der(19)t(17;19)(q23;p13). *Mol Cytogenet.* 2013;6:40. DOI: 10.1186/1755-8166-6-40.

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57 **Genetic terms.** Café-au-lait spots. This image is a derivative work, adapted from the following source, available under : Dumitrescu CE and Collins MT. *Orphanet J Rare Dis.* 2008;3:12. DOI: 10.1186/1750-1172-3-12.

61 **Muscular dystrophies.** Fibrofatty replacement of muscle. Courtesy of the Department of Health and Human Services and Dr. Edwin P. Ewing, Jr. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

66 **Vitamin A.** Bitot sponts on conjunctiva. This image is a derivative work, adapted from the following source, available under : Baiyeroju A, Bowman R, Gilbert C, et al. Managing eye health in young children. *Comm Eye Health.* 2010;23(72):4-11. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2873666.

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70 **Vitamin D.** X-ray of lower extremity in child with rickets. This image is a derivative work, adapted from the following source, available

under : Dr. Michael L. Richardson. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

71 **Protein-energy malnutrition: Image A.** Child with kwashiorkor. Courtesy of the Department of Health and Human Services and Dr. Lyle Conrad.

71 **Protein-energy malnutrition: Image B.** Child with marasmus. Courtesy of the Department of Health and Human Services.

84 **Alkaptonuria.** Pigment granules on dorsum of hand. This image is a derivative work, adapted from the following source, available under : Vasudevan B, Sawhney MPS, Radhakrishnan S. Alkaptonuria associated with degenerative collagenous palmar plaques. *Indian J Dermatol.* 2009;54:299-301. DOI: 10.4103/0019-5154.55650.

85 **Cystinuria.** Hexagonal cystine stones in urine. This image is a derivative work, adapted from the following source, available under : Courtesy of Cayla Devine.

88 **Lysosomal storage diseases: Image A.** "Cherry-red" spot on macula in Tay-Sachs disease. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Jonathan Trobe.

88 **Lysosomal storage diseases: Image B.** Angiokeratomas. This image is a derivative work, adapted from the following source, available under : Burlina AP, Sims KB, Politei JM, et al. Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel. *BMC Neurol.* 2011;11:61. DOI: 10.1186/1471-2377-11-61. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

88 **Lysosomal storage diseases: Image C.** Gaucher cells in Gaucher disease. This image is a derivative work, adapted from the following source, available under : Sokołowska B, Skomra D, Czartoryska B. et al. Gaucher disease diagnosed after bone marrow trephine biopsy—a report of two cases. *Folia Histochem Cytobiol.* 2011;49:352-356. DOI: 10.5603/FHC.2011.0048. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

88 **Lysosomal storage diseases: Image D.** Foam cells in Niemann-Pick disease. This image is a derivative work, adapted from the following source, available under : Prieto-Potin I, Roman-Blas JA, Martinez-Calatrava MJ, et al. Hypercholesterolemia boosts joint destruction in chronic arthritis. An experimental model aggravated by foam macrophage infiltration. *Arthritis Res Ther.* 2013;15:R81. DOI: 10.1186/ar4261.

94 **Abetalipoproteinemia.** Small bowel mucosa shows clear enterocytes. Courtesy of Dr. Michael Bonert.

## Immunology

96 **Lymph node: Images A and B.** Lymph node histology. These images are a derivative work, adapted from the following source, available under : Navid Golpur.

98 **Thymus.** "Sail sign" on x-ray of normal thymus in neonate. This image is a derivative work, adapted from the following source, available under : Di Serafino M, Esposito F, Severino R, et al. Think thymus, think well: the chest x-ray thymic signs. *J Pediatr Moth Care.* 2016;1(2):108-109. DOI: 10.19104/japm.2016.108.

107 **Complement disorders.** Urine discoloration in paroxysmal nocturnal hemoglobinuria. This image is a derivative work, adapted from the following source, available under : Nakamura N, Sugawara T, Shirato K, et al. *J Med Case Reports.* 2011;5:550. doi: 10.1186/1752-1947-5-550

117 **Immunodeficiencies: Image A.** Spider angioma (telangiectasia). This image is a derivative work, adapted from the following source, available under : Liapakis IE, Englander M, Sinani R, et al. Management of facial telangiectasias with hand cautery. *World J Plast Surg.* 2015 Jul;4(2):127-133.

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## Microbiology

125 **Stains: Image A.** *Trypanosoma lewisi* on Giemsa stain. Courtesy of the Department of Health and Human Services and Dr. Mae Melvin.

125 **Stains: Image B.** Periodic acid–Schiff stain reveals *Tropheryma whipplei* infection. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Ed Uthman.

125 **Stains: Image C.** *Mycobacterium tuberculosis* on Ziehl-Neelsen stain. Courtesy of the Department of Health and Human Services and Dr. George P. Kubica.

125 **Stains: Image D.** *Cryptococcus neoformans* on India ink stain. Courtesy of the Department of Health and Human Services.

125 **Stains: Image E.** *Coccidioides immitis* on silver stain. Courtesy of the Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.

127 **Encapsulated bacteria.** Capsular swelling of *Streptococcus pneumoniae* using the Neufeld-Quellung test. Courtesy of the Department of Health and Human Services.

128 **Catalase-positive organisms.** Oxygen bubbles released during catalase reaction. This image is a derivative work, adapted from the following source, available under : Stefano Nase. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

129 **Spore-forming bacteria.** This image is a derivative work, adapted from the following source, available under : Jones SW, Paredes CJ, Tracy B. The transcriptional program underlying the physiology of clostridial sporulation. *Genome Biol.* 2008;9:R114. DOI: 10.1186/gb-2008-9-7-r114.

135 **α-hemolytic bacteria.** α-hemolysis. This image is a derivative work, adapted from the following source, available under : Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

135 **β-hemolytic bacteria.** β-hemolysis. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons.

135 ***Staphylococcus aureus.*** Courtesy of the Department of Health and Human Services and Dr. Richard Facklam.

136 ***Streptococcus pneumoniae.*** Courtesy of the Department of Health and Human Services and Dr. Mike Miller.

136 ***Streptococcus pyogenes:* (group A streptococci).** This image is a derivative work, adapted from the following source, available under : Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

137 ***Bacillus anthracis.*** Ulcer with black eschar. Courtesy of the Department of Health and Human Services and James H. Steele.

138 **Clostridia: Image A.** Gas gangrene due to *Clostridium perfringens*. This image is a derivative work, adapted from the following source, available under : Schröpfer E, Rauthe S, Meyer T. Diagnosis and misdiagnosis of necrotizing soft tissue infections: three case reports. *Cases J.* 2008;1:252. DOI: 10.1186/1757-1626-1-252.

**138 Clostridia: Image B.** Pseudomembranous enterocolitis on colonoscopy. This image is a derivative work, adapted from the following source, available under : Klinikum Dritter Orden für die Überlassung des Bildes zur Veröffentlichu. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**139 *Corynebacterium diphtheriae*.** Pseudomembranous pharyngitis. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**139 *Listeria monocytogenes*.** Actin rockets. This image is a derivative work, adapted from the following source, available under : Schuppler M, Loessner MJ. The opportunistic pathogen *Listeria monocytogenes*: pathogenicity and interaction with the mucosal immune system. *Int J Inflamm.* 2010;2010:704321. DOI: 10.4061/2010/704321. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**139 *Nocardia* vs *Actinomyces*: Image A.** *Nocardia* on acid-fast stain. This image is a derivative work, adapted from the following source, available under : Venkataramana K. Human *Nocardia* infections: a review of pulmonary nocardiosis. *Cereus.* 2015;7(8):e304. DOI: 10.7759/cureus.304.

**139 *Nocardia* vs *Actinomyces*: Image B.** *Actinomyces israelii* on Gram stain. Courtesy of the Department of Health and Human Services.

**140 Mycobacteria.** Acid-fast stain. Courtesy of the Department of Health and Human Services and Dr. George P. Kubica

**140 Tuberculosis.** Langhans giant cell in caseating granuloma. Courtesy of J. Hayman.

**141 Leprosy: Image A.** "Glove and stocking" distribution. This image is a derivative work, adapted from the following source, available under : Courtesy of Bruno Jehle.

**142 *Neisseria*: Image A.** Intracellular *N gonorrhoeae*. Courtesy of the Department of Health and Human Services and Bill Schwartz.

**142 *Haemophilus influenzae*: Image A.** Epiglottitis. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**143 *Legionella pneumophila*.** Lung findings of unilateral and lobar infiltrate. This image is a derivative work, adapted from the following source, available under : Robbins NM, Kumar A, Blair BM. *Legionella pneumophila* infection presenting as headache, confusion and dysarthria in a human immunodeficiency virus-1 (HIV-1) positive patient: case report. *BMC Infect Dis.* 2012;12:225. DOI: 10.1186/1471-2334-12-225.

**143 *Pseudomonas aeruginosa*: Image A.** Blue-green pigment on centrimide agar. This image is a derivative work, adapted from the following source, available under : Hansen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**143 *Pseudomonas aeruginosa*: Image B.** Ecthyma gangrenosum. This image is a derivative work, adapted from the following source, available under : Uludokumaci S, Balkan II, Mete B, et al. Ecthyma gangrenosum-like lesions in a febrile neutropenic patient with simultaneous *Pseudomonas* sepsis and disseminated fusariosis. *Turk J Haematol.* 2013 Sep;30(3):321-4. DOI: 10.4274/Tjh.2012.0030.

**145 *Klebsiella*.** Courtesy of the Department of Health and Human Services.

**145 *Campylobacter jejuni*.** Courtesy of the Department of Health and Human Services.

**146 *Vibrio cholerae*.** This image is a derivative work, adapted from the following source, available under : Phetsouvanh R, Nakatsu M, Arakawa E, et al. Fatal bacteremia due to immotile *Vibrio cholerae* serogroup O21 in Vientiane, Laos—a case report. *Ann Clin Microbiol Antimicrob.* 2008;7:10. DOI: 10.1186/1476-0711-7-10.

**146 *Helicobacter pylori*.** Courtesy of the Department of Health and Human Services, Dr. Patricia Fields, and Dr. Collette Fitzgerald.

**146 Spirochetes.** Appearance on darkfield microscopy. Courtesy of the Department of Health and Human Services.

**146 Lyme disease: Image A.** *Ixodes* tick. Courtesy of the Department of Health and Human Services and Dr. Michael L. Levin.

**146 Lyme disease: Image B.** Erythema migrans. Courtesy of the Department of Health and Human Services and James Gathany.

**147 Syphilis: Image A.** Painless chancre in primary syphilis. Courtesy of the Department of Health and Human Services and M. Rein.

**147 Syphilis: Image B.** Treponeme on darkfield microscopy. Courtesy of the Department of Health and Human Services and Renelle Woodall.

**147 Syphilis: Image D.** Rash on palms. This image is a derivative work, adapted from the following source, available under : Drahansky M, Dolezel M, Urbanek J, et al. Influence of skin diseases on fingerprint recognition. *J Biomed Biotechnol.* 2012;626148. DOI: 10.1155/2012/626148.

**147 Syphilis: Image E.** Condyloma lata. Courtesy of the Department of Health and Human Services and Susan Lindsley.

**147 Syphilis: Image F.** Gumma. This image is a derivative work, adapted from the following source, available under : Chakir K, Benchikhi H. Granulome centro-facial révélant une syphilis tertiaire. *Pan Afr Med J.* 2013;15:82. DOI: 10.11604/pamj.2013.15.82.3011.

**147 Syphilis: Image G.** Congenital syphilis. Courtesy of the Department of Health and Human Services and Dr. Norman Cole.

**147 Syphilis: Image H.** Hutchinson teeth. Courtesy of the Department of Health and Human Services and Susan Lindsley.

**148 *Gardnerella vaginalis*.** Courtesy of the Department of Health and Human Services and M. Rein.

**150 Rickettsial diseases and vector-borne illnesses: Image A.** Rash of Rocky Mountain spotted fever. Courtesy of the Department of Health and Human Services.

**150 Rickettsial diseases and vector-borne illnesses: Image B.** *Ehrlichia* morulae. This image is a derivative work, adapted from the following source, available under : Dantas-Torres F. Canine vector-borne diseases in Brazil. *Parasit Vectors.* 2008;1:25. DOI: 10.1186/1756-3305-1-25. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**150 Rickettsial diseases and vector-borne illnesses: Image C.** *Anaplasma phagocytophilium* in neutrophil. Courtesy of the Department of Health and Human Services and Dumler JS, Choi K, Garcia-Garcia JC, et al. Human granulocytic anaplasmosis. *Emerg Infect Dis.* 2005. DOI 10.3201/eid1112.050898.

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**151 Systemic mycoses: Image A.** *Histoplasma*. Courtesy of the Department of Health and Human Services and Dr. D.T. McClenan.

**151 Systemic mycoses: Image B.** *Blastomyces dermatitidis* undergoing broad-base budding. Courtesy of the Department of Health and Human Services and Dr. Libero Ajello.

151 **Systemic mycoses: Image C.** Coccidiomycosis with endospheres. Courtesy of the Department of Health and Human Services.

151 **Systemic mycoses: Image D.** "Captain's wheel" shape of *Paracoccidioides.*. Courtesy of the Department of Health and Human Services and Dr. Lucille K. Georg.

152 **Cutaneous mycoses: Image G.** Tinea versicolor. This image is a derivative work, adapted from the following source, available under : Sarah (Rosenau) Korf. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

153 **Opportunistic fungal infections: Image A.** Budding yeast of *Candida albicans.* This image is a derivative work, adapted from the following source, available under : Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

153 **Opportunistic fungal infections: Image B.** Germ tubes of *Candida albicans.*. This image is a derivative work, adapted from the following source, available under : Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

153 **Opportunistic fungal infections: Image C.** Oral thrush. Courtesy of the Department of Health and Human Services and Dr. Sol Silverman, Jr.

153 **Opportunistic fungal infections: Image E.** Conidiophores of *Aspergillus fumigatus.* Courtesy of the Department of Health and Human Services.

153 **Opportunistic fungal infections: Image F.** Aspergilloma in left lung. This image is a derivative work, adapted from the following source, available under : Souilamas R, Souilamas JI, Alkhamees K, et al. Extra corporal membrane oxygenation in general thoracic surgery: a new single veno-venous cannulation. *J Cardiothorac Surg.* 2011;6:52. DOI: 10.1186/1749-8090-6-52.

153 **Opportunistic fungal infections: Image G.** *Cryptococcus neoformans.* Courtesy of the Department of Health and Human Services and Dr. Leanor Haley.

153 **Opportunistic fungal infections: Image H.** *Cryptococcus neoformans* on mucicarmine stain. Courtesy of the Department of Health and Human Services and Dr. Leanor Haley.

153 **Opportunistic fungal infections: Image I.** Mucor. Courtesy of the Department of Health and Human Services and Dr. Lucille K. Georg.

153 **Opportunistic fungal infections: Image J.** Mucormycosis. This image is a derivative work, adapted from the following source, available under : Jiang N, Zhao G, Yang S, et al. A retrospective analysis of eleven cases of invasive rhino-orbito-cerebral mucormycosis presented with orbital apex syndrome initially. *BMC Ophthalmol.* 2016; 16: 10. DOI: 10.1186/s12886-016-0189-1.

154 ***Pneumocystis jirovecii*: Image A.** Interstitial opacities in lung. This image is a derivative work, adapted from the following source, available under : Chuang C, Zhanhong X, Yinyin G, et al. Unsuspected *Pneumocystis* pneumonia in an HIV-seronegative patient with untreated lung cancer: circa case report. *J Med Case Rep.* 2007;1:15. DOI: 10.1186/1752-1947-1-115.

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154 ***Pneumocystis jiroveci*: Image C.** Disc-shaped yeast. This image is a derivative work, adapted from the following source, available under : Kirby S, Satoskar A, Brodsky S, et al. Histological spectrum of pulmonary manifestations in kidney transplant recipients on sirolimus inclusive immunosuppressive regimens. *Diagn Pathol.* 2012;7:25. DOI: 10.1186/1746-1596-7-25.

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155 **Protozoa—gastrointestinal infections: Image B.** *Giardia lamblia* cyst. Courtesy of the Department of Health and Human Services.

155 **Protozoa—gastrointestinal infections: Image C.** *Entamoeba histolytica* trophozoites. Courtesy of the Department of Health and Human Services.

155 **Protozoa—gastrointestinal infections: Image D.** *Entamoeba histolytica* cyst. Courtesy of the Department of Health and Human Services.

155 **Protozoa—gastrointestinal infections: Image E.** *Cryptosporidium* oocysts. Courtesy of the Department of Health and Human Services.

156 **Protozoa—CNS infections: Image A.** Ring-enhancing lesions in brain due to *Toxoplasma gondii.* This image is a derivative work, adapted from the following source, available under : Agrawal A, Bhake A, Sangole VM, et al. Multiple-ring enhancing lesions in an immunocompetent adult. *J Glob Infect Dis.* 2010 Sep-Dec;2(3):313-4. DOI: 10.4103/0974-777X.68545.

156 **Protozoa—CNS infections: Image B.** *Toxoplasma gondii* tachyzoite. Courtesy of the Department of Health and Human Services and Dr. L.L. Moore, Jr.

156 **Protozoa—CNS infections: Image C.** *Naegleria fowleri* amoebas. Courtesy of the Department of Health and Human Services.

156 **Protozoa—CNS infections: Image D.** *Trypanosoma brucei gambiense.* Courtesy of the Department of Health and Human Services and Dr. Mae Melvin.

157 **Protozoa—hematologic infections: Image A.** *Plasmodium* trophozoite ring form. Courtesy of the Department of Health and Human Services.

157 **Protozoa—hematologic infections: Image B.** *Plasmodium* schizont containing merozoites. Courtesy of the Department of Health and Human Services and Steven Glenn.

157 **Protozoa—hematologic infections: Image C.** *Babesia* with ring form and with "Maltese cross" form. Courtesy of the Department of Health and Human Services.

158 **Protozoa—others: Image A.** *Trypanosoma cruzi.* Courtesy of the Department of Health and Human Services and Dr. Mae Melvin.

158 **Protozoa—others: Image B.** Cutaneous leishmaniasis. This image is a derivative work, adapted from the following source, available under : Sharara SL, Kanj SS. War and infectious diseases: challenges of the Syrian civil war. *PLoS Pathog.* 2014 Nov;10(11):e1004438. DOI: 10.1371/journal.ppat.1004438.

158 **Protozoa—others: Image C.** *Leishmania* spp. Courtesy of the Department of Health and Human Services and Dr. Francis W. Chandler. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

158 **Protozoa—others: Image D.** *Trichomonas vaginalis.* Courtesy of the Department of Health and Human Services.

159 **Nematodes (roundworms): Image A.** *Enterobius vermicularis* eggs. Courtesy of the Department of Health and Human Services, BG Partin, and Dr. Moore.

**159 Nematodes (roundworms): Image B.** *Ascaris lumbricoides* egg. Courtesy of the Department of Health and Human Services.

**159 Nematodes (roundworms): Image C.** *Ancylostoma* spp rash. This image is a derivative work, adapted from the following source, available under : Archer M. Late presentation of cutaneous larva migrans: a case report. *Cases J.* 2009; 2: 7553. doi:10.4076/1757-1626-2-7553.

**159 Nematodes (roundworms): Image D.** *Trichinella spiralis* cysts in muscle. This image is a derivative work, adapted from the following source, available under : Franssen FFJ, Fonville M, Takumi K, et al. *Vet Res.* 2011; 42(1): 113. DOI: 10.1186/1297-9716-42-113.

**159 Nematodes (roundworms): Image E.** Elephantiasis. Courtesy of the Department of Health and Human Services.

**160 Cestodes (tapeworms): Image A.** *Taenia solium*. Courtesy of the Department of Health and Human Services Robert J. Galindo. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**160 Cestodes (tapeworms): Image B.** Neurocysticercosis. This image is a derivative work, adapted from the following source, available under : Coyle CM, Tanowitz HB. Diagnosis and treatment of neurocysticercosis. *Interdiscip Perspect Infect Dis.* 2009;2009:180742. DOI: 10.1155/2009/180742. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**160 Cestodes (tapeworms): Image C.** *Echinococcus granulosus*. Courtesy of the Department of Health and Human Services.

**160 Cestodes (tapeworms): Image D.** Hyatid cyst of *Echinococcus granulosus*. Courtesy of the Department of Health and Human Services and Dr. I. Kagan.

**160 Cestodes (tapeworms): Image E.** *Echinococcus granulosus* cyst in liver. This image is a derivative work, adapted from the following source, available under : Ma Z, Yang W, Yao Y, et al. The adventitia resection in treatment of liver hydatid cyst: a case report of a 15-year-old boy. *Case Rep Surg.* 2014;2014:123149. DOI: 10.1155/2014/123149.

**160 Trematodes (flukes): Image A.** *Schistosoma mansoni* egg with lateral spine. Courtesy of the Department of Health and Human Services.

**160 Trematodes (flukes): Image B.** *Schistosoma haematobium* egg with terminal spine. Courtesy of the Department of Health and Human Services.

**161 Ectoparasites: Image A.** Scabies. This image is a derivative work, adapted from the following source, available under : Siegfried EC, Hebert AA. Diagnosis of atopic dermatitis: mimics, overlaps, and complications. *Clin Med.* 2015 May; 4(5): 884–917. DOI: 10.3390/jcm4050884.

**161 Ectoparasites: Image B.** Nit of a louse. Courtesy of the Department of Health and Human Services and Joe Miller.

**164 DNA viruses.** Febrile pharyngitis. This image is a derivative work, adapted from the following source, available under : Balfour HH Jr, Dunmire SK, Hogquist KA. *Clin Transl Immunology.*2015 Feb 27. DOI: 10.1038/cti.2015.1.

**165 Herpesviruses: Image A.** Keratoconjunctivitis in HSV-1 infection. This image is a derivative work, adapted from the following source, available under : Yang HK, Han YK, Wee WR, et al. Bilateral herpetic keratitis presenting with unilateral neurotrophic keratitis in pemphigus foliaceus: a case report. *J Med Case Rep.* 2011;5:328. DOI: 10.1186/1752-1947-5-328.

**165 Herpesviruses: Image B.** Herpes labialis. Courtesy of the Department of Health and Human Services and Dr. Herrmann.

**165 Herpesviruses: Image E.** Shingles (varicella-zoster virus infection). This image is a derivative work, adapted from the following source, available under : Fisle. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**165 Herpesviruses: Image F.** Hepatosplenomegaly due to EBV infection. This image is a derivative work, adapted from the following source, available under : Gow NJ, Davidson RN, Ticehurst R, et al. Case report: no response to liposomal daunorubicin in a patient with drug-resistant HIV-associated visceral leishmaniasis. *PLoS Negl Trop Dis.* 2015 Aug; 9(8):e0003983. DOI: 10.1371/journal.pntd.0003983.

**165 Herpesviruses: Image G.** Atypical lymphocytes in Epstein-Barr virus infection. This image is a derivative work, adapted from the following source, available under : Coutesy of Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**165 Herpesviruses: Image I.** Roseola. Courtesy of Emiliano Burzagli.

**165 Herpesviruses: Image J.** Kaposi sarcoma. Courtesy of the Department of Health and Human Services.

**166 HSV identification.** Positive Tzanck smear in HSV-2 infection. This image is a derivative work, adapted from the following source, available under : Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**168 Rotavirus.** Courtesy of the Department of Health and Human Services and Erskine Palmer.

**169 Rubella virus.** Rubella rash. Courtesy of the Department of Health and Human Services.

**170 Acute laryngotracheobronchitis.** Steeple sign. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.

**170 Measles (rubeola) virus: Image A.** Koplik spots. Courtesy of the Department of Health and Human Services. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**170 Measles (rubeola) virus: Image B.** Rash of measles. Courtesy of the Department of Health and Human Services.

**170 Mumps virus.** Swollen neck and parotid glands. Courtesy of the Department of Health and Human Services.

**171 Rabies virus: Image A.** Transmission electron micrograph. Courtesy of the Department of Health and Human Services Dr. Fred Murphy, and Sylvia Whitfield.

**171 Rabies virus: Image B.** Negri bodies. Courtesy of the Department of Health and Human Services and Dr. Daniel P. Perl.

**171 Ebola virus.** Courtesy of the Department of Health and Human Services and Cynthia Goldsmith.

**172 Zika virus.** This image is a derivative work, adapted from the following source, available under : Rocha YRR, Costa JRC, Costa PA, et al. Radiological characterization of cerebral phenotype in newborn microcephaly cases from 2015 outbreak in Brazil. *PLoS Currents* 2016 Jun 8;8. DOI: 10.1371/currents.outbreaks.e854dbf51b8075431a05b39042c00244.

**180 Osteomyelitis.** X-ray (left) and MRI (right) views. This image is a derivative work, adapted from the following source, available under : Huang P-Y, Wu P-K, Chen C-F, et al. Osteomyelitis of the femur mimicking bone tumors: a review of 10 cases. *World J Surg Oncol.* 2013;11:283. DOI: 10.1186/1477-7819-11-283.

**181 Common vaginal infections: Image B.** Motile trichomonads. Courtesy of Joe Miller.

**181 Common vaginal infections: Image C.** *Candida* vulvovaginitis. Courtesy of Mikael Häggström.

**182 TORCH infections: Image A.** “Blueberry muffin” rash. This image is a derivative work, adapted from the following source, available under

: Benmiloud S, Elhaddou G, Belghiti ZA, et al. Blueberry muffin syndrome. *Pan Afr Med J.* 2012;13:23.

**182 TORCH infections: Image B.** Cataract in infant with contenital rubella. Courtesy of the Department of Health and Human Services .

**182 TORCH infections: Image C.** Periventricular calcifications in congenital cytomegalovirus infection. This image is a derivative work, adapted from the following source, available under : Bonthius D, Perlman S. Congenital viral infections of the brain: lessons learned from lymphocytic choriomeningitis virus in the neonatal rat. *PLoS Pathog.* 2007;3:e149. DOI: 10.1371/journal.ppat.0030149. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**183 Red rashes of childhood: Image C.** Child with scarlet fever. This image is a derivative work, adapted from the following source, available under : www.badobadop.co.uk.

**183 Red rashes of childhood: Image D.** Chicken pox. Courtesy of the Department of Health and Human Services and Dr. JD Millar.

**184 Sexually transmitted infections: Image A.** Chancroid. Courtesy of the Department of Health and Human Services and Dr. Greg Hammond.

**184 Sexually transmitted infections: Image B.** Donovanosis. Courtesy of the Department of Health and Human Services and Dr. Pinozzi.

**185 Pelvic inflammatory disease: Image A.** Purulent cervical discharge. This image is a derivative work, adapted from the following source, available under : SOS-AIDS Amsterdam The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**185 Pelvic inflammatory disease: Image B.** Adhesions in Fitz-Hugh–Curtis syndrome. Courtesy of Hic et nunc.

**190 Vancomycin.** Red man syndrome. This image is a derivative work, adapted from the following source, available under : O'Meara P, Borici-Mazi R, Morton R, et al. DRESS with delayed onset acute interstitial nephritis and profound refractory eosinophilia secondary to vancomycin. *Allergy Asthma Clin Immunol.* 2011;7:16. DOI: 10.1186/1710-1492-7-16.

## Pathology

**209 Necrosis: Image A.** Coagulative necrosis. Courtesy of the Department of Health and Human Services and Dr. Steven Rosenberg.

**209 Necrosis: Image B.** Liquefactive necrosis. Courtesy of Daftblogger.

**209 Necrosis: Image C.** Caseous necrosis. This image is a derivative work, adapted from the following source, available under : Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**209 Necrosis: Image D.** Fat necrosis. This image is a derivative work, adapted from the following source, available under : Patho. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**209 Necrosis: Image E.** Fibrinoid necrosis. This image is a derivative work, adapted from the following source, available under : Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**209 Necrosis: Image F.** Acral gangrene. Courtesy of the Department of Health and Human Services and William Archibald.

**210 Ischemia.** This image is a derivative work, adapted from the following source, available under : Van Assche LM, Kim HW, Jensen CJ, et al. A new CMR protocol for non-destructive, high resolution, ex-vivo assessment of the area at risk simultaneous with infarction: validation with histopathology. *J Cardiovasc Magn Reson.* 2012; 14(Suppl 1): O7. DOI: 10.1186/1532-429X-14-S1-O7.

**210 Types of infarcts: Image B.** Pale infarct. Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.

**212 Types of calcification.** Dystrophic calcification. This image is a derivative work, adapted from the following source, available under : Chun J-S, Hong R, Kim J-A. Osseous metaplasia with mature bone formation of the thyroid gland: three case reports. *Oncol Lett.* 2013;6:977-979. DOI: 10.3892/ol.2013.1475. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**212 Lipofuscin.** This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**213 Amyloidosis: Image A.** Amyloid deposits on Congo red stain. This image is a derivative work, adapted from the following source, available under : Dr. Ed Uthman.

**213 Amyloidosis: Image B.** Apple green birefringence under polarized light. This image is a derivative work, adapted from the following source, available under : Dr. Ed Uthman.

**215 Acute inflammation.** Pericardium with severe inflammation, neutrophilic infiltration and fibrin with entrapped clusters of bacteria. This image is a derivative work, adapted from the following source, available under : Faida Ajili, et al. Coexistence of pyoderma gangrenosum and sweet's syndrome in a patient with ulcerative colitis. *Pan Afr Med J.* 2015 Jun 24. DOI: 10.11604/pamj.2015.21.151.6364.

**218 Granulomatous diseases.** Granuloma. Courtesy of Sanjay Mukhopadhyay.

**219 Scar formation: Image A.** Hypertrophic scar. This image is a derivative work, adapted from the following source, available under : Baker R, Urso-Baiarda F, Linge C, et al. Cutaneous scarring: a clinical review. *Dermatol Res Pract.* 2009;2009:625376. DOI: 10.1155/2009/625376.

**219 Scar formation: Image B.** Keloid scar. This image is a derivative work, adapted from the following source, available under : Dr. Andreas Settje. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**220 Neoplasia and neoplastic progression.** Cervical tissue. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**224 Common metastases: Image A.** Brain metastases from breast cancer. This image is a derivative work, adapted from the following source, available under : Jmarchn. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**224 Common metastases: Image B.** Brain metastasis. Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.

**224 Common metastases: Image C.** Liver metastasis. This image is a derivative work, adapted from the following source, available under : Dr. James Heilman The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**224 Common metastases: Image D.** Liver metastasis. Courtesy of J. Hayman.

**224 Common metastases: Image E.** Bone metastasis. This image is a derivative work, adapted from the following source, available under : Dr. Paul Hellerhoff.

**224 Common metastases: Image F.** Bone metastasis. This image is a derivative work, adapted from the following source, available under : Courtesy of M Emmanuel.

**228 Psammoma bodies.** Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.

## Cardiovascular

**292 Anatomy of the heart: Image A.** MRI showing normal cardiac anatomy. This image is a derivative work, adapted from the following source, available under : Zhang J, Chen L, Wang X, et al. Compounding local invariant features and global deformable geometry for medical image registration. *PLoS One.* 2014;9(8):e105815. DOI: 10.1371/journal.pone.0105815.

**292 Anatomy of the heart: Image B.** X-ray showing normal cardiac anatomy. This image is a derivative work, adapted from the following source, available under : Karippacheril JG, Joseph TT. Negative pressure pulmonary oedema and haemorrhage, after a single breath-hold: Diaphragm the culprit? *Indian J Anaesth.* 2010 Jul-Aug;54(4):361–363. DOI: 10.4103/0019-5049.68391.

**306 Congenital heart diseases: Image A.** "Egg on string" appearance on x-ray of the chest in D-transposition of the great vessels. This image is a derivative work, adapted from the following source, available under : Aloriany IA, Barlas NB, Al-Boukai AA. Pictorial essay: Infants of diabetic mothers. *Indian J Radiol Imaging.* 2010 Aug;20(3):174–181. DOI: 10.4103/0971-3026.69349.

**306 Congenital heart diseases: Image B.** Tetralogy of Fallot. This image is a derivative work, adapted from the following source, available under : Rashid AKM: Heart diseases in Down syndrome. In: Dey S, ed: Down syndrome. DOI: 10.5772/46009. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**307 Congenital heart diseases: Image C.** Ventricular septal defect. This image is a derivative work, adapted from the following source, available under : Bardo DME, Brown P. Cardiac multidetector computed tomography: basic physics of image acquisition and clinical applications. *Curr Cardiol Rev.* 2008 Aug;4(3):231–243. DOI: 10.2174/157340308785160615.

**307 Congenital heart diseases: Image D.** Atrial septal defect. This image is a derivative work, adapted from the following source, available under : Teo KSL, Dundon BK, Molaee P, et al. Percutaneous closure of atrial septal defects leads to normalisation of atrial and ventricular volumes. *J Cardiovasc Magn Reson.* 2008;10(1):55. DOI: 10.1186/1532-429X-10-55.

**307 Congenital heart diseases: Image E.** Patent ductus arteriosus. This image is a derivative work, adapted from the following source, available under : Henjes CR, Nolte I, Wesfaedt P. Multidetector-row computed tomography of thoracic aortic anomalies in dogs and cats: patent ductus arteriosus and vascular rings. *BMC Vet Res.* 2011;7:57. DOI: 10.1186/1746-6148-7-57.

**307 Congenital heart diseases: Image F.** MRI showing coarctation of the aorta. This image is a derivative work, adapted from the following source, available under : Vergales JE, Gangemi JJ, Rhueban KS, Lim DS. Coarctation of the aorta — the current state of surgical and transcatheter therapies. *Curr Cardiol Rev.* 2013 Aug; 9(3): 211–219. DOI: 10.2174/1573403X113099990032

**308 Hypertension.** "String of beads" appearance in fibromuscular dysplasia. This image is a derivative work, adapted from the following source, available under : Plouin PF, Perdu J, LaBatide-Alanore A, et al. Fibromuscular dysplasia. *Orphanet J Rare Dis.* 2007;7:28. DOI: 10.1186/1750-1172-2-28. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**309 Hyperlipidemia signs: Image C.** Tendinous xanthoma. This image is a derivative work, adapted from the following source, available under : Raffa W, Hassam B. Xanthomes tendineux et tubéreux révélant une hypercholestérolémie familiale. *Pan Afr Med J.* 2013; 15: 49. DOI: 10.11604/pamj.2013.15.49.2636.

**309 Arteriosclerosis: Image A.** Hyaline type. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**309 Arteriosclerosis: Image B.** Hyperplastic type. This image is a derivative work, adapted from the following source, available under : Paco Larosa. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**309 Arteriosclerosis: Image C.** Monckeberg sclerosis (medial calcific sclerosis). This image is a derivative work, adapted from the following source, available under : Couri CE, da Silva GA, Martinez JA, et al. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**311 Aortic dissection.** This image is a derivative work, adapted from the following source, available under : Qi Y, Ma X, Li G, et al. Three-dimensional visualization and imaging of the entry tear and intimal flap of aortic dissection using CT virtual intravascular endoscopy. *PLoS One.* 2016; 11(10): e0164750. DOI: 10.1371/journal.pone.0164750.

**313 Evolution of myocardial infarction: Images A and B.** Heart tissue at 0-24 hours (image A) and 1-3 days (image B) after myocardial infarction. These images are a derivative work, adapted from the following source, available under : Chang J, Nair V, Luk A, et al. Pathology of myocardial infarction. *Diagn Histopath.* 2013;19:7-12. DOI: https://doi.org/10.1016/j.mpdhp.2012.11.001.

**313 Evolution of myocardial infarction: Image C.** Heart tissue 3-14 days after myocardial infarction. This image is a derivative work, adapted from the following source, available under : Diarmid AK, Pellicori P, Cleland JG, et al. Taxonomy of segmental myocardial systolic dysfunction. *Eur Heart J.* 2017 Apr 1;38(13):942–954. DOI: 10.1093/eurheartj/ehw140.

**313 Evolution of myocardial infarction: Image D.** Heart tissue after myocardial infarction showing dense fibrous scar replacing myocyte loss. This image is a derivative work, adapted from the following source, available under : Michaud K, Basso C, d'Amati G, et al on behalf of the Association for European Cardiovascular Pathology. Diagnosis of myocardial infarction at autopsy: AECVP reappraisal in the light of the current clinical classification. *Virchows Arch.* 2020;476:179–194.

**317 Myocardial infarction complications: Image A.** Papillary muscle rupture. This image is a derivative work, adapted from the following source, available under : Routy B, Huynh T, Fraser R, et al. Vascular endothelial cell function in catastrophic antiphospholipid syndrome: a case report and review of the literature. *Case Rep Hematol.* 2013;2013:710365. DOI: 10.1155/2013/710365.

**317 Myocardial infarction complications: Image B.** Drawing of pseudoaneurysm. This image is a derivative work, adapted from the following source, available under : Patrick J. Lynch and Dr. C. Carl Jaffe.

**317 Myocardial infarction complications: Image C.** Free wall rupture of left ventricle. This image is a derivative work, adapted from the following source, available under : Zacarias ML, da Trindade H, Tsutsu J, et al. Left ventricular free wall impeding rupture in post-myocardial infarction period diagnosed by myocardial contrast echocardiography: case report. *Cardiovasc Ultrasound.* 2006;4:7. DOI: 10.1186/1476-7120-4-7.

**318 Cardiomyopathies: Image A.** Dilated cardiomyopathy. This image is a derivative work, adapted from the following source, available under : Gho JMIH, van Es R, Stathonikos N, et al. High resolution systematic digital histological quantification of cardiac fibrosis and

adipose tissue in phospholamban p.Arg14del mutation associated cardiomyopathy. *PLoS One.* 2014;9:e94820. DOI: 10.1371/journal.pone.0094820.

**318 Cardiomyopathies: Image B.** Hypertrophic obstructive cardiomyopathy. This image is a derivative work, adapted from the following source, available under : Benetti MA, Belo Nunes RA, Benvenuti LA. Case 2/2016 - 76-year-old male with hypertensive heart disease, renal tumor and shock. *Arq Bras Cardiol.* 2016 May; 106(5): 439–446. DOI: 10.5935/abc.20160067.

**319 Heart failure.** Pedal edema. This image is a derivative work, adapted from the following source, available under : Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**320 Cardiac tamponade: Image A.** CT showing cardiac tamponade. This image is a derivative work, adapted from the following source, available under : Yousuf T, Kramer J, Kopiec A, et al. A rare case of cardiac tamponade induced by chronic rheumatoid arthritis. *J Clin Med Res.* 2015 Sep;7(9):720–723. DOI: 10.14740/jocmr2226w.

**320 Cardiac tamponade: Image B.** ECG showing cardiac tamponade. This image is a derivative work, adapted from the following source, available under : Maharaj SS, Chang SM. Cardiac tamponade as the initial presentation of systemic lupus erythematosus: a case report and review of the literature. *Pediatr Rheumatol Online J.* 2015; 13: 9. DOI: 10.1186/s12969-015-0005-0.

**321 Bacterial endocarditis: Image A.** Vegetations on heart valves. Courtesy of the Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.

**321 Bacterial endocarditis: Image C.** Osler nodes. This image is a derivative work, adapted from the following source, available under : Yang ML, Chen YH, Lin WR, et al. Case report: infective endocarditis caused by Brevundimonas vesicularis. *BMC Infect Dis.* 2006;6:179. DOI: 10.1186/1471-2334-6-179.

**321 Bacterial endocarditis: Image D.** Janeway lesions on sole. This image is a derivative work, adapted from the following source, available under : Courtesy of DeNanneke.

**322 Rheumatic fever.** Aschoff body and Anitschkow cells. This image is a derivative work, adapted from the following source, available under : Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**323 Acute pericarditis.** This image is a derivative work, adapted from the following source, available under : Bogaert J, Francone M. Cardiovascular magnetic resonance in pericardial diseases. *J Cardiovasc Magn Reson.* 2009;11:14. DOI: 10.1186/1532-429X-11-14. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

## Endocrine

**334 Thyroid development.** Thyroglossal duct cyst. This image is a derivative work, adapted from the following source, available under : Adelchi C, Mara P, Melissa L, et al. Ectopic thyroid tissue in the head and neck: a case series. *BMC Res Notes.* 2014;7:790. DOI: 10.1186/1756-0500-7-790.

**348 Hypothyroidism vs hyperthyroidism: Image A.** Pretibial myxedema. This image is a derivative work, adapted from the following source, available under : Fred H, van Dijk HA. Images of memorable cases: case 144. Connexions Web site. Dec 8, 2008. Available at: https://cnx.org/contents/SCJeD6JM@3/Images-of-Memorable-Cases-Case-144.

**348 Hypothyroidism vs hyperthyroidism: Image B.** Onycholysis. This image is a derivative work, adapted from the following source, available under : Alborz Fallah. This image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**348 Hypothyroidism vs hyperthyroidism: Image C.** Periorbital myxedema. This image is a derivative work, adapted from the following source, available under : Dandekar F, Camacho M, Valerio J, et al. *Case Rep Ophthalmol Med.* 2015;2015:126501. DOI: 10.1155/2015/126501.

**349 Hypothyroidism: Image B.** Hashimoto thyroiditis histology. This image is a derivative work, adapted from the following source, available under : Librepath. This image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**349 Hypothyroidism: Image C.** Subacute granulomatous thyroiditis histology. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. This image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**349 Hypothyroidism: Image E.** Before and after treatment of congenital hypothyroidism. Courtesy of the Department of Health and Human Services.

**349 Hypothyroidism: Image F.** Congenital hypothyroidism. This image is a derivative work, adapted from the following source, available under : Sadasiv Swain. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**350 Thyroid adenoma.** This image is a derivative work, adapted from the following source, available under : Terada T. Brain metastasis from thyroid adenomatous nodules or an encapsulated thyroid follicular tumor without capsular and vascular invasion: a case report. *Cases J.* 2009; 2: 7180. DOI: 10.4076/1757-1626-2-7180.

**352 Hypoparathyroidism.** Shortened 4th and 5th digits. This image is a derivative work, adapted from the following source, available under : Ferrario C, Gastaldi G, Portmann L, et al. Bariatric surgery in an obese patient with Albright hereditary osteodystrophy: a case report. *J Med Case Rep.* 2013; 7: 111. DOI: 10.1186/1752-1947-7-111.

**353 Hyperparathyroidism.** Multiple lytic lesions. This image is a derivative work, adapted from the following source, available under : Khaoula BA, Kaouther BA, Ines C, et al. An unusual presentation of primary hyperparathyroidism: pathological fracture. *Case Rep Orthop.* 2011;2011:521578. DOI: 10.1155/2011/521578. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**357 Adrenal insufficiency.** Mucosal hyperpigmentation in primary adrenal insufficiency. Courtesy of FlatOut. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**359 Pheochromocytoma.** This image is a derivative work, adapted from the following source, available under : Dr. Michael Feldman.

**360 Multiple endocrine neoplasias.** Mucosal neuroma. This image is a derivative work, adapted from the following source, available under : Martucciello G, Lerone M, Bricco L, et al. Multiple endocrine neoplasias type 2B and RET proto-oncogene. *Ital J Pediatr.* 2012;38:9. DOI: 10.1186/1824-7288-38-9.

**361 Carcinoid syndrome.** Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.

## Gastrointestinal

**368 Ventral wall defects: Image A.** Gastroschisis. This image is a derivative work, adapted from the following source, available under : Zvizdic Z. Gastroschisis with concomitant jejuno-ileal atresia complicated by jejunal perforation. *J Neonatal Surg.* 2016 Apr-Jun; 5(2): 25.

**368 Ventral wall defects: Image B.** Omphalocele. This image is a derivative work, adapted from the following source, available under : Khan YA, Qureshi MA, Akhtar J. Omphalomesenteric duct cyst

in an omphalocele: a rare association. *Pak J Med Sci.* 2013 May-Jun; 29(3): 866–868.

368 **Ventral wall defects.** Drawings of gastroschisis (left) and omphalocele (right). Courtesy of the Department of Health and Human Services.

368 **Ventral wall defects: Image C.** Congenital diaphragmatic hernia. This image is a derivative work, adapted from the following source, available under : Rastogi MV, LaFranchi SH. Congenital hypothyroidism. *Orphanet J Rare Dis.* 2010;5:17. DOI: 10.1186/1750-1172-5-17.

369 **Intestinal atresia.** This image is a derivative work, adapted from the following source, available under : Saha M. Alimentary tract atresias associated with anorectal malformations: 10 years' experience. *J Neonatal Surg.* 2016 Oct-Dec; 5(4): 43. DOI: 10.21699/jns.v5i4.449.

369 **Hypertrophic pyloric stenosis.** This image is a derivative work, adapted from the following source, available under : Hassan RAA, Choo YU, Noraida R, et al. Infantile hypertrophic pyloric stenosis in postoperative esophageal atresia with tracheoesophageal fistula. *J Neonatal Surg.* 2015 Jul-Sep;4(3):32.

370 **Pancreas and spleen embryology.** Annular pancreas. This image is a derivative work, adapted from the following source, available under : Mahdi B, Selim S, Hassen T, et al. A rare cause of proximal intestinal obstruction in adults—annular pancreas: a case report. *Pan Afr Med J.* 2011;10:56. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

370 **Retroperitoneal structures.** This image is a derivative work, adapted from the following source, available under : Sammut J, Ahiaku E, Williams DT. Complete regression of renal tumour following ligation of an accessory renal artery during repair of an abdominal aortic aneurysm. *Ann R Coll Surg Engl.* 2012 Sep; 94(6): e198–e200. DOI: 10.1308/003588412X13373405384972.

372 **Digestive tract anatomy.** Histology of stomach wall. This image is a derivative work, adapted from the following source, available under : Alexander Klepnev.

372 **Digestive tract histology: Image A.** Gastric glands Courtesy of Dr. Michale Bonert.

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387 **Esophageal pathologies: Image B.** Esophageal varices on endoscopy. This image is a derivative work, adapted from the following source, available under : Costaguta A, Alvarez F. Etiology and management of hemorrhagic complications of portal hypertension in children. *Int J Hepatol.* 2012;2012:879163. DOI: 10.1155/2012/879163.

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390 **Ulcer complications.** Free air under diaphragm in perforated ulcer. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.

391 **Malabsorption syndromes: Image A.** Celiac disease. This image is a derivative work, adapted from the following source, available under : Celiac disease. Sedda S, Caruso R, Marafini I, et al. Pyoderma gangrenosum in refractory celiac disease: a case report. *BMC Gastroenterol.* 2013; 13: 162. DOI: 10.1186/1471-230X-13-162.

391 **Malabsorption syndromes: Image B.** *Tropheryma whippeli* on PAS stain. This image is a derivative work, adapted from the following source, available under : Tran HA. Reversible hypothyroidism and Whipple's disease. *BMC Endocr Disord.* 2006;6:3. DOI: 10.1186/1472-6823-6-3.

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associated with liver cirrhosis and hepatocellular carcinoma. *Hum Mutat.* 2016 Oct; 37(10): 1097–1105.DOI: 10.1002/humu.23047.

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## Hematology and Oncology

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429 **Microcytic, hypochromic anemia: Image D.** Lead lines in lead poisoning. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.

429 **Microcytic, hypochromic anemia: Image E.** Sideroblastic anemia. This image is a derivative work, adapted from the following source, available under : Paulo Henrique Orlandi Moura. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

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434 **Heme synthesis, porphyrias, and lead poisoning: Image B.** Porphyria cutanea tarda. This image is a derivative work, adapted from the following source, available under : Bovenschen HJ, Vissers WHPM. Primary hemochromatosis presented by porphyria cutanea tarda: a case report. *Cases J.* 2009;2:7246. DOI: 10.4076/1757-1626-2-7246.

435 **Coagulation disorders.** Hemarthrosis. This image is a derivative work, adapted from the following source, available under : Lakjiri S, Mernissi FZ. Tabetic arthropathy revealing neurosyphilis: a new observation. *Pan Afr Med J.* 2014; 18: 198. DOI: 10.11604/pamj.2014.18.198.4893.

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439 **Non-Hodgkin lymphoma: Image B.** Jaw lesion in Burkitt lymphoma. This image is a derivative work, adapted from the following source, available under : Bi CF, Tang Y, Zhang WY, et al. Sporadic Burkitt lymphomas of children and adolescents in Chinese: a clinicopathological study of 43 cases. *Diagn Pathol.* 2012;7:72. DOI:10.1186/1746-1596-7-72.

439 **Non-Hodgkin lymphoma: Image C.** Primary CNS lymphoma. This image is a derivative work, adapted from the following source, available under : Mansour A, Qandeel M, Abdel-Razeq H, et al. MR imaging features of intracranial primary CNS lymphoma in immune competent patients. *Cancer Imaging.* 2014;14(1):22. DOI: 10.1186/1470-7330-14-22.

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440 **Plasma cell dyscrasias: Image C.** This image is a derivative work, adapted from the following source, available under : Mehrotra R, Singh M, Singh PA, et al. Should fine needle aspiration biopsy be the first pathological investigation in the diagnosis of a bone lesion? An algorithmic approach with review of literature. *Cytojournal.* 2007; 4: 9. DOI: 10.1186/1742-6413-4-9.

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443 **Myeloproliferative neoplasms: Image A.** Erythromelalgia in polycythemia vera. This image is a derivative work, adapted from the following source, available under : Fred H, van Dijk H. Images of memorable cases: case 151. Connexions Web site. December 4, 2008. Available at http://cnx.org/content/m14932/1.3/.

443 **Myeloproliferative neoplasms: Image C.** Myelofibrosis. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Ed Uthman.

444 **Langerhans cell histiocytosis: Image A.** Lytic bone lesion. This image is a derivative work, adapted from the following source, available under : Dehkordi NR, Rajabi P, Naimi A, et al. Langerhans cell histiocytosis following Hodgkin lymphoma: a case report from Iran. *J Res Med Sci.* 2010;15:58-61. PMCID PMC3082786.

444 **Langerhans cell histiocytosis: Image B.** Birbeck granules. This image is a derivative work, adapted from the following source, available under : Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

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## Musculoskeletal, Skin, and Connective Tissue

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458 **Brachial plexus lesions: Image A.** Cervical rib. This image is a derivative work, adapted from the following source, available under : Dahlin LB, Backman C, Duppe H, et al. Compression of the lower trunk of the brachial plexus by a cervical rib in two adolescent girls: case reports and surgical treatment. *J Brachial Plex Peripher Nerve Inj.* 2009;4:14. DOI: 10.1186/1749-7221-4-14.

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477 **Primary bone tumors: Image C.** Giant cell tumor. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.

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480 **Sjögren syndrome: Image B.** Dry tongue. This image is a derivative work, adapted from the following source, available under : Negrato CA, Tarzia O. Buccal alterations in diabetes mellitus. *Diabetol Metab Syndr.* 2010;2:3. DOI: 10.1186/1758-5996-2-3.

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481 **Seronegative spondyloarthropathies: Image C, right.** Bamboo spine.  Courtesy of Heather Hawker.

483 **Polymyositis/dermatomyositis: Image A.** Groton papules of dermatomyositis. This image is a derivative work, adapted from the following source, available under : *Pan Afr Med J*.2015; 21: 89. DOI: 10.11604/pamj.2015.21.89.6971.

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485 **Vasculitides: Image B.** Angiogram in patient with Takayasu arteritis.  Courtesy of the Department of Health and Human Services and Justin Ly.

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485 **Vasculitides: Image E.** Coronary artery aneurysm in Kawasaki disease. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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485 **Vasculitides: Image H.** Granulomatosis with polyangiitis (formerly Wegener) and PR3-ANCA/c-ANCA.  Courtesy of M.A. Little.

485 **Vasculitides: Image I.** Henoch-Schönlein purpura.  Courtesy of Okwikikim.

485 **Vasculitides: Image J.** MPO-ANCA/p-ANCA in microscopic polyangiitis.  Courtesy of and M.A. Little.

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**492 Vascular tumors of skin: Image C.** Glomus tumor under fingernail. This image is a derivative work, adapted from the following source, available under: Hazani R, Houle JM, Kasdan ML, et al. Glomus tumors of the hand. *Eplasty.* 2008;8:e48. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**493 Skin infections: Image C.** Erysipelas. This image is a derivative work, adapted from the following source, available under: Courtesy of Klaus D. Peter.

**494 Autoimmune blistering skin disorders: Image D.** Bullous pemphigoid on immunofluorescence. This image is a derivative work, adapted from the following source, available under: Courtesy of M. Emmanuel.

**495 Lower extremity ulcers: Image A.** Venous ulcer. This image is a derivative work, adapted from the following source, available under: Motolese A, Vignati F, Brambilla R, et al. Interaction between a regenerative matrix and wound bed in nonhealing ulcers: results with 16 cases. *Biomed Res Int.* 2013;849321. DOI: 10.1155/2013/849321.

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## Neurology and Special Senses

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**506 Posterior fossa malformations: Image A.** Chiari I malformation. This image is a derivative work, adapted from the following source, available under: Toldo I, De Carlo D, Mardari R, et al. Short lasting activity-related headaches with sudden onset in children: a case-based reasoning on classification and diagnosis. *J Headache Pain.* 2013;14(1):3. DOI: 10.1186/1129-2377-14-3.

**506 Posterior fossa malformations: Image B.** Dandy-Walker malformation. This image is a derivative work, adapted from the following source, available under: Krupa K, Bekiesinska-Figatowska M. Congenital and acquired abnormalities of the corpus callosum: a pictorial essay. *Biomed Res Int.* 2013;2013:265619. DOI: 10.1155/2013/265619.

**506 Syringomyelia.** Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.

**508 Myelin.** Myelinated neuron. Courtesy of the Electron Microscopy Facility at Trinity College.

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**531 Intracranial hemorrhage: Image E.** Subarachnoid hemorrhage. This image is a derivative work, adapted from the following source, available under: Hakan T, Turk CC, Celik H. Intra-operative real time intracranial subarachnoid haemorrhage during glial tumour resection: a case report. *Cases J.* 2008;1:306. DOI: 10.1186/1757-1626-1-306. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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J, et al. Rapid identification of a major diffusion/perfusion mismatch in distal internal carotid artery or middle cerebral artery ischemic stroke. *BMC Neurol.* 2012 Nov 5;12:132. DOI: 10.1186/1471-2377-12-132. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

533 **Effects of strokes: Image B.** Lacunar infarct of lenticulostriate artery. This image is a derivative work, adapted from the following source, available under : Zhou L, Ni J, Yao M, et al. High-resolution MRI findings in patients with capsular warning syndrome. *BMC Neurol.* 2014;14:16. DOI: 10.1186/1471-2377-14-16.

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543 **Neurocutaneous disorders: Image E.** Angiomyolipoma in tuberous sclerosis. This image is a derivative work, adapted from the following source, available under : KGH. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

543 **Neurocutaneous disorders: Image F.** Café-au-lait spots in neurofibromatosis. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

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incidentally detected by thyroid ultrasonography: a case report. *J Med Case Rep.* 2012;6:179. DOI: 10.1186/1752-1947-6-179.

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543 **Neurocutaneous disorders: Image J.** Brainstem and spinal cord hemangioblastomas in von Hippel-Lindau disease. This image is a derivative work, adapted from the following source, available under : Park DM, Zhuang Z, Chen L, et al. von Hippel-Lindau disease-associated hemangioblastomas are derived from embryologic multipotent cells. *PLoS Med.* 2007 Feb;4(2):e60. DOI: 10.1371/journal.pmed.0040060.

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544 **Adult primary brain tumors: Image C.** Oligodendroglioma in frontal lobes. This image is a derivative work, adapted from the following source, available under : Celzo FG, Venstermans C, De Belder F, et al. Brain stones revisited—between a rock and a hard place. *Insights Imaging.* 2013 Oct;4(5):625-35. DOI: 10.1007/s13244-013-0279-z.

544 **Adult primary brain tumors: Image D.** Oligodendroglioma, "fried egg" cells. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

544 **Adult primary brain tumors: Image E.** Meningioma with dural tail. This image is a derivative work, adapted from the following source, available under : Smits A, Zetterling M, Lundin M, et al. Neurological impairment linked with cortico-subcortical infiltration of diffuse low-grade gliomas at initial diagnosis supports early brain plasticity. *Front Neurol.* 2015;6:137. DOI: 10.3389/fneur.2015.00137.

544 **Adult primary brain tumors: Image F.** Meningioma, psammoma bodies. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

544 **Adult primary brain tumors: Image G.** Cerebellar hemangioblastoma. This image is a derivative work, adapted from the following source, available under : Park DM, Zhengping Z, Chen L, et al. von Hippel-Lindau disease-associated hemangioblastomas are derived from embryologic multipotent cells. *PLoS Med.* 2007 Feb;4(2):e60. DOI: 10.1371/journal.pmed.0040060.

544 **Adult primary brain tumors: Image H.** Minimal parenchyma in hemangioblastoma. This image is a derivative work, adapted from the following source, available under : Marvin 101. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

545 **Adult primary brain tumors: Image I.** Field of vision in bitemporal hemianopia. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

545 **Adult primary brain tumors: Image J.** Prolactinoma. This image is a derivative work, adapted from the following source, available under : Wang CS, Yeh TC, Wu TC, et al. Pituitary macroadenoma co-existent with supraclinoid internal carotid artery cerebral aneurysm: a case report and review of the literature. *Cases J.* 2009;2:6459. DOI: 10.4076/1757-1626-2-6459.

545 **Adult primary brain tumors: Image K.** Schwannoma at cerebellopontine angle.  Courtesy of MRT-Bild.

545 **Adult primary brain tumors: Image L.** Schwannoma. This image is a derivative work, adapted from the following source, available under : Shah AA, Latoo S, Ahmad I, et al. Schwannoma causing resorption of zygomatic arch. *J Oral Maxillofac Pathol.* 2011;15(1):80–84. DOI: 10.4103/0973-029X.80020.

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546 **Childhood primary brain tumors: Image C.** CT of medulloblastoma.  Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.

546 **Childhood primary brain tumors: Image D.** Medulloblastoma histology. This image is a derivative work, adapted from the following source, available under : KGH. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

546 **Childhood primary brain tumors: Image E.** MRI of ependymoma. This image is a derivative work, adapted from the following source, available under : Dr. Paul Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

546 **Childhood primary brain tumors: Image F.** Ependymoma histology. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

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549 **Friedreich ataxia.** Clinical kyphoscoliosis. This image is a derivative work, adapted from the following source, available under : Axelrod FB, Gold-von Simson. Hereditary sensory and autonomic neuropathies: types II, III, and IV. *Orphanet J Rare Dis.* 2007;2:39. DOI: 10.1186/1750-1172-2-39.

550 **Facial nerve lesions.** Facial nerve palsy. This image is a derivative work, adapted from the following source, available under : Socolovsky M, Paez MD, Di Masi G, et al. Bell's palsy and partial hypoglossal to facial nerve transfer: Case presentation and literature review. *Surg Neurol Int.* 2012;3:46. DOI: 10.4103/2152-7806.95391.

552 **Cholesteatoma.** This image is a derivative work, adapted from the following source, available under : Welleschik. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

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553 **Conjunctivitis.** This image is a derivative work, adapted from the following source, available under : Baiyeroju A, Bowman R,

Gilbert C, et al. Managing eye health in young children. *Community Eye Health.* 2010;23:4-11.

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**555 Glaucoma: Image D.** Acute angle closure glaucoma. This image is a derivative work, adapted from the following source, available under :. Courtesy of Dr. Jonathan Trobe.

**555 Uveitis.** This image is a derivative work, adapted from the following source, available under : Weber AC, Levison AL, Srivastava, et al. A case of *Listeria monocytogenes* endophthalmitis with recurrent inflammation and novel management. *J Ophthalmic Inflamm Infect.* 2015;5(1):28. DOI: 10.1186/s12348-015-0058-8.

**556 Age-related macular degeneration.** Courtesy of the Department of Health and Human Services.

**556 Diabetic retinopathy.** This image is a derivative work, adapted from the following source, available under : Sundling V, Gulbrandsen P, Straand J. Sensitivity and specificity of Norwegian optometrists' evaluation of diabetic retinopathy in single-field retinal images – a cross-sectional experimental study. *BMC Health Services Res.* 2013;13:17. DOI: 10.1186/1472-6963-13-17.

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**557 Retinal detachment.** Courtesy of EyeRounds.

**557 Retinitis pigmentosa.** Courtesy of EyeRounds.

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**560 Ocular motility.** Blowout fracture of orbit with entrapment of superior rectus muscle. This image is a derivative work, adapted from the following source, available under : Gonzalez MO, Durairaj VD. Indirect orbital floor fractures: a meta-analysis. *Middle East Afr J Ophthalmol.* 2010;17(2):138–141. DOI: 10.4103/0974-9233.63076.

**561 CN III, IV, VI palsies: Image A.** Cranial nerve III damage. This image is a derivative work, adapted from the following source, available under : Hakim W, Sherman R, Rezk T, et al. An acute case of herpes zoster ophthalmicus with ophthalmoplegia. *Case Rep Ophthalmol Med.* 1012; 2012:953910. DOI: 10.1155/2012/953910.

**561 CN III, IV, VI palsies: Image B.** Cranial nerve IV damage. This image is a derivative work, adapted from the following source, available under : Mendez JA, Arias CR, Sanchez D, et al. Painful ophthalmoplegia of the left eye in a 19-year-old female, with an emphasis in Tolosa-Hunt syndrome: a case report. *Cases J.* 2009; 2: 8271. DOI: 10.4076/1757-1626-2-8271.

**561 CN III, IV, VI palsies: Image C.** Cranial nerve VI damage. This image is a derivative work, adapted from the following source, available under : Jordi March i Nogué. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

## Psychiatry

**586 Trichotillomania.** Courtesy of Robodoc.

## Renal

**602 Potter sequence.** Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.

**603 Horseshoe kidney.** This image is a derivative work, adapted from the following source, available under : Rispoli P, Destefanis P, Garneri P, et al. Inferior vena cava prosthetic replacement in a patient with horseshoe kidney and metastatic testicular tumor: technical considerations and review of the literature. *BMC Urol.* 2014;14:40. DOI: 10.1186/1471-2490-14-40.

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**605 Course of ureters.** This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

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**620 Nephritic syndrome: Image A.** Histology of acute poststreptococcal glomerulonephritis. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**620 Nephritic syndrome: Image B.** Immunofluorescence of acute poststreptococcal glomerulonephritis. This image is a derivative work, adapted from the following source, available under : Immunofluorescence of acute poststreptococcal glomerulonephritis. Oda T, Yoshizawa N, Yamakami K, et al. The role of nephritis-associated plasmin receptor (naplr) in glomerulonephritis associated with streptococcal infection. *Biomed Biotechnol.* 2012;2012:417675. DOI 10.1155/2012/417675.

**620 Nephritic syndrome: Image C.** Histology of rapidly progressive glomerulonephritis. Courtesy of the Department of Health and Human Services and Uniformed Services University of the Health Sciences.

620 **Nephritic syndrome: Image D.** "Tram tracks" in membranoproliverative glomerulonephritis. This image is a derivative work, adapted from the following source, available under : Kiremitci S, Ensari A. Classifying lupus nephritis: an ongoing story. *Scientific World Journal.* 2014; 2014: 580620. DOI: 10.1155/2014/580620.

621 **Nephrotic syndrome: Image A.** Effacement of podocyte foot processes in minimal change disease. This image is a derivative work, adapted from the following source, available under : Teoh DCY, El-Modir A. Managing a locally advanced malignant thymoma complicated by nephrotic syndrome: a case report. *J Med Case Reports.* 2008; 2: 89. DOI: 10.1186/1752-1947-2-89.

621 **Nephrotic syndrome: Image B.** Histology of focal segmental glomerulosclerosis. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

621 **Nephrotic syndrome: Image D.** Diabetic glomerulosclerosis with Kimmelstiel-Wilson lesions. This image is a derivative work, adapted from the following source, available under : Doc Mari. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

622 **Kidney stones: Image A.** Nair S, George J, Kumar S, et al. Acute oxalate nephropathy following ingestion of *Averrhoa bilimbi* juice. *Case Rep Nephrol.* 2014; 2014: DOI: 10.1155/2014/240936.

622 **Kidney stones: Image B.** This image is a derivative work, adapted from the following source, available under : Joel Mills. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

623 **Hydronephrosis.** Ultrasound. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

624 **Pyelonephritis: Image A.** This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

624 **Pyelonephritis: Image B.** CT scan. Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.

626 **Acute tubular necrosis: Image A.** Muddy brown casts. This image is a derivative work, adapted from the following source, available under : Dr. Serban Nicolescu.

626 **Renal papillary necrosis.** Courtesy of the Department of Health and Human Services and William D. Craig, Dr. Brent J. Wagner, and Mark D. Travis.

627 **Renal cyst disorders: Image C.** Ultrasound of simple cyst. This image is a derivative work, adapted from the following source, available under : Nevit Dilmen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

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629 **Renal oncocytoma: Image A.** Gross specimen. This image is a derivative work, adapted from the following source, available under : Courtesy of M. Emmanuel.

629 **Renal oncocytoma: Image B.** Histology. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

629 **Nephroblastoma.** This image is a derivative work, adapted from the following source, available under : Refaie H, Sarhan M, Hafez A. Role of CT in assessment of unresectable Wilms tumor response after preoperative chemotherapy in pediatrics. *Sci World J.* 2008;8:661-669. doi 10.1100/tsw.2008.96.

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## Reproductive

639 **Fetal alcohol syndrome.** This image is a derivative work, adapted from the following source, available under : Courtesy of Teresa Kellerman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

642 **Umbilical cord: Image A.** Cross-section of umbilical cord. This image is a derivative work, adapted from the following source, available under : Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

642 **Umbilical cord: Image B.** Meckel diverticulum. This image is a derivative work, adapted from the following source, available under : Mathur P, Gupta R, Simlot A, et al. Congenital pouch colon with double Meckel's diverticulae. *J Neonatal Surg.* 2013 Oct-Dec; 2(4): 48.

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650 **Female reproductive epithelial histology.** Transformation zone. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

652 **Seminiferous tubules.** This image is a derivative work, adapted from the following source, available under : Dr. Anlt Rao. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

665 **Pregnancy complications.** Ectopic pregnancy. This image is a derivative work, adapted from the following source, available under : Li W, Wang G, Lin T, et al. Misdiagnosis of bilateral tubal pregnancy: a case report. *J Med Case Rep.* 2014;8:342. DOI: 10.1186/1752-1947-8-342.

666 **Hydatidiform mole: Image A.** Cluster of cluster of grapes appearance in complete hydatidiform mole. This image is a derivative work, adapted from the following source, available under : Dr. Ed Uthman

**666 Choriocarcinoma: Image B.** "Cannonball" metastases. This image is a derivative work, adapted from the following source, available under : Lekanidi K, Vlachou PA, Morgan B, et al. Spontaneous regression of metastatic renal cell carcinoma: case report. *J Med Case Rep.* 2007;1:89. DOI: 10.1186/1752-1947-1-89.

**668 Vulvar pathology: Image A.** Bartholin cyst. Courtesy of the Department of Health and Human Services and Susan Lindsley.

**668 Vulvar pathology: Image B.** Lichen sclerosis. This image is a derivative work, adapted from the following source, available under : Lambert J. Pruritus in female patients. *Biomed Res Int.* 2014;2014:541867. DOI: 10.1155/2014/541867.

**668 Vulvar pathology: Image C.** Vulvar carcinoma. This image is a derivative work, adapted from the following source, available under : Ramli I, Hassam B. Carcinome épidermoïde vulvaire: pourquoi surveiller un lichen scléro-atrophique. *Pan Afr Med J.* 2015;21:48. DOI: 10.11604/pamj.2015.21.48.6018.

**668 Vulvar pathology: Image D.** Extramallary Paget disease. This image is a derivative work, adapted from the following source, available under : Wang X, Yang W, Yang J. Extramammary Paget's disease with the appearance of a nodule: a case report. *BMC Cancer.* 2010;10:405. DOI: 10.1186/1471-2407-10-405.

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**671 Ovarian tumors: Image C.** Dysgerminoma. This image is a derivative work, adapted from the following source, available under : Montesinos L, Acien P, Martinez-Beltran M, et al. Ovarian dysgerminoma and synchronic contralateral tubal pregnancy followed by normal intra-uterine gestation: a case report. *J Med Rep.* 2012;6:399. DOI: 10.1186/1752-1947-6-399.

**671 Ovarian tumors: Image D.** Mature cystic teratoma. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**671 Ovarian tumors: Image E.** Yolk sac tumor. This image is a derivative work, adapted from the following source, available under : Jensflorian. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**671 Ovarian tumors: Image F.** Call-Exner bodies. This image is a derivative work, adapted from the following source, available under : Katoh T, Yasuda M, Hasegawa K, et al. Estrogen-producing endometrioid adenocarcinoma resembling sex cord-stromal tumor of the ovary: a review of four postmenopausal cases. *Diagn Pathol.* 2012;7:164. DOI: 10.1186/1746-1596-7-164.

**672 Uterine conditions: Image A.** Endometrial tissue found outside the uterus. This image is a derivative work, adapted from the following source, available under : Hastings JM, Fazleabas AT. A baboon model for endometriosis: implications for fertility. *Reprod Biol Endocrinol.* 2006;4(suppl 1):S7. DOI: 10.1186/1477-7827-4-S1-S7.

**672 Uterine conditions: Image B.** Endometritis with inflammation of the endometrium. This image is a derivative work, adapted from the following source, available under : Montesinos L, Acien P, Martinez-Beltran M, et al. Ovarian dysgerminoma and synchronic contralateral tubal pregnancy followed by normal intra-uterine gestation: a case report. *J Med Rep.* 2012;6:399. DOI: 10.1186/1752-1947-6-399.

**672 Uterine conditions: Image C.** Endometrial carcinoma. This image is a derivative work, adapted from the following source, available under : Izadi-Mood N, Yarmohammadi M, Ahmadi SA, et al. Reproducibility determination of WHO classification of endometrial hyperplasia/well differentiated adenocarcinoma and comparison with computerized morphometric data in curettage specimens in Iran. *Diagn Pathol.* 2009;4:10. DOI:10.1186/1746-1596-4-10.

**672 Uterine conditions: Image D.** Leiomyoma (fibroid), gross specimen. This image is a derivative work, adapted from the following source, available under : Courtesy of Hic et nunc.

**672 Uterine conditions: Image E.** Leiomyoma (fibroid) histology. This image is a derivative work, adapted from the following source, available under : Londero AP, Perego P, Mangioni C, et al. Locally relapsed and metastatic uterine leiomyoma: a case report. *J Med Case Rep.* 2008;2:308. DOI: 10.1186/1752-1947-2-308. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**673 Benign breast disease: Image A.** Fibroadenomas. This image is a derivative work, adapted from the following source, available under : Gokhale S. Ultrasound characterization of breast masses. *Indian J Radiol Imaging.* 2009 Aug;19(3):242-7. DOI: 10.4103/0971-3026.54878.

**673 Benign breast disease: Images B and C.** Phyllodes tumor (B) and phyllodes cyst (C) on ultrasound. These images are a derivative work, adapted from the following source, available under : Muttarak MD, Lerttumnongtum P, Somwangjaroen A, et al. Phyllodes tumour of the breast. *Biomed Imaging Interv J.* 2006 Apr-Jun;2(2):e33. DOI: 10.2349/biij.2.2.e33.

**674 Breast cancer: Image A.** Mammography of breast cancer. This image is a derivative work, adapted from the following source, available under : Molino C, Mocerino C, Braucci A, et al. Pancreatic solitary and synchronous metastasis from breast cancer: a case report and systematic review of controversies in diagnosis and treatment. World J Surg Oncol. 2014;12:2. DOI:10.1186/1477-7819-12-2

**674 Breast cancer: Image C.** Comedocarcinoma. This image is a derivative work, adapted from the following source, available under : Costarelli L, Campagna D, Mauri M, et al. Intraductal proliferative lesions of the breast—terminology and biology matter: premalignant lesions or preinvasive cancer? *Int J Surg Oncol.* 2012;501904. DOI: 10.1155/2012/501904. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**674 Breast cancer: Image D.** Paget disease of breast. This image is a derivative work, adapted from the following source, available under : Muttarak M, Siriya B, Kongmebhol P, et al. Paget's disease of the breast: clinical, imaging and pathologic findings: a review of 16 patients. *Biomed Imaging Interv J.* 2011;7:e16. DOI: 10.2349/biij.7.2.e16.

**674 Breast cancer: Image E.** Invasive lobular carcinoma. This image is a derivative work, adapted from the following source, available under : Franceschini G, Manno A, Mule A, et al. Gastro-intestinal symptoms as clinical manifestation of peritoneal and retroperitoneal spread of an invasive lobular breast cancer: report of a case and review of the literature. *BMC Cancer.* 2006;6:193. DOI: 10.1186/1471-2407-6-193.

**674 Breast cancer: Image F.** Peau d'orange of inflammatory breast cancer. This image is a derivative work, adapted from the following source, available under : Levine PH, Zolfaghari L, Young H, et al. What Is inflammatory breast cancer? Revisiting the case definition. *Cancers (Basel).* 2010 Mar;2(1):143–152. DOI: 10.3390/cancers2010143.

**675 Penile pathology: Image A.** Peyronie disease. This image is a derivative work, adapted from the following source, available under : Tran VQ, Kim DH, Lesser TF, et al. Review of the surgical approaches for Peyronie's disease: corporeal plication and plaque incision with grafting. *Adv Urol.* 2008; 2008: 263450. DOI: 10.1155/2008/263450.

**675 Penile pathology: Image B.** Squamous cell carcinoma. This image is a derivative work, adapted from the following source, available under : Antônio JR, Antônio CR, Trídico LA. Erythroplasia of queyrat

treated with topical 5-fluorouracil. *An Bras Dermatol.* 2016 Sep-Oct; 91(5 Suppl 1): 42–44. DOI: 10.1590/abd1806-4841.20164595.

**675 Cryptorchidism.** This image is a derivative work, adapted from the following source, available under : Pandey A, Gangopadhyay AN, Kumar V. High anorectal malformation in a five-month-old boy: a case report. *J Med Case Reports.* 2010; 4: 296. DOI: 10.1186/1752-1947-4-296.

**675 Varicocele.** This image is a derivative work, adapted from the following source, available under : Mak CW, Tzeng WS. Sonography of the scrotum. DOI: 10.5772/27586.

**676 Benign scrotal lesions.** Congenital hydrocele. This image is a derivative work, adapted from the following source, available under : Leonardi S, Barone P, Gravina G, et al. Severe Kawasaki disease in a 3-month-old patient: a case report. *BMC Res Notes.* 2013;6:500. DOI: 10.1186/1756-0500-6-500.

## Respiratory

**685 Alveolar cell types: Image A.** Electron micrograph of type II pneumocyte. This image is a derivative work, adapted from the following source, available under : Fehrenbach H, Tews S, Fehrenbach A, et al. Improved lung preservation relates to an increase in tubular myelin-associated surfactant protein A. *Respir Res.* 2005 Jun 21;6:60. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**685 Alveolar cell types: Image B.** Micrograph of type II pneumocyte. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Thomas Caceci.

**685 Neonatal respiratory distress syndrome.** This image is a derivative work, adapted from the following source, available under : Alorainy IA, Balas NB, Al-Boukai AA. Pictorial essay: infants of diabetic mothers. *Indian J Radiol Imaging.* 2010;20:174-181. DOI: 10.4103/0971-3026.69349.

**687 Lung anatomy: Image A.** X-ray of normal lung. This image is a derivative work, adapted from the following source, available under : Namkoong H, Fujiwara H, Ishii M, et al. Immune reconstitution inflammatory syndrome due to *Mycobacterium avium* complex successfully followed up using 18 F-fluorodeoxyglucose positron emission tomography-computed tomography in a patient with human immunodeficiency virus infection: A case report. *BMC Med Imaging.* 2015;15:24. DOI 10.1186/s12880-015-0063-2.

**687 Lung anatomy: Image B.** CT scan of the chest. This image is a derivative work, adapted from the following source, available under : Wang JF, Wang B, Jansen JA, et al. Primary squamous cell carcinoma of lung in a 13-year-old boy: a case report. *Cases J.* 2008 Aug 22;1(1):123. DOI: 10.1186/1757-1626-1-123. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

**691 Cyanide vs carbon monoxide poisoning.** FLAIR axial image showing bilateral symmetrical basal ganglia lesions in patients with carbon monoxide poisoning. This image is a derivative work, adapted from the following source, available under : Subhaschandra S, Jatishwor W, Suraj Th. Isolated symmetrical bilateral basal ganglia T2 hyperintensity in carbon monoxide poisoning. *Ann Indian Acad Neurol.* 2008 Oct-Dec; 11(4): 251–253. DOI: 10.4103/0972-2327.44563.

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**695 Deep venous thrombosis.**This image is a derivative work, adapted from the following source, available under : Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**696 Pulmonary emboli: Image B.** CT scan. This image is a derivative work, adapted from the following source, available under : Dr. Carl Chartrand-Lefebvre. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**699 Obstructive lung diseases: Image A.** Barrel-shaped chest in emphysema. This image is a derivative work, adapted from the following source, available under : Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**699 Obstructive lung diseases: Image B.** Lung tissue with enlarged alveoli in emphysema. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert.

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**699 Obstructive lung diseases: Image D.** Emphysema histology. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**699 Obstructive lung diseases: Image E.** Mucus plugs in asthma. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**699 Obstructive lung disease: Image F.** Curschmann spirals. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under . Dr. James Heilman.

**699 Obstructive lung diseases: Image G.** Charcot-Leyden crystals on bronchalverolar lavage. This image is a derivative work, adapted from the following source, available under : Gholamnejad M, Rezaie N. Unusual presentation of chronic eosinophilic pneumonia with "reversed halo sign": a case report. *Iran J Radiol.* 2014 May;11(2):e7891. DOI: 10.5812/iranjradiol.7891.

**699 Obstructive lung disease: Image H.** Bronchiectasis in cystic fibrosis. This image is a derivative work, adapted from the following source, available under : Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**700 Sarcoidosis: Image A.** Kajal B, Harvey J, Alowami S. Melkerrson-Rosenthal Syndrome, a rare case report of chronic eyelid swelling. *Diagn Pathol.* 2013; 8: 188. DOI: 10.1186/1746-1596-8-188.

**700 Sarcoidosis: Images B and C.** X-ray (B) and CT (C) of the chest. These images are a derivative work, adapted from the following source, available under : Lønborg J, Ward M, Gill A, et al. Utility of cardiac magnetic resonance in assessing right-sided heart failure in sarcoidosis. *BMC Med Imaging.* 2013;13:2. DOI: 10.1186/1471-2342-13-2.

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**701 Pneumoconioses: Image A.** Pleural plaques in asbestosis. This image is a derivative work, adapted from the following source, available under : Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

**701 Pneumoconioses: Image B.** CT scan of asbestosis. This image is a derivative work, adapted from the following source, available under : Miles SE, Sandrini A, Johnson AR, et al. Clinical consequences

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704 **Digital clubbing.** This image is a derivative work, adapted from the following source, available under : Desherinka. This image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

704 **Atelectasis.** This image is a derivative work, adapted from the following source, available under : Khan AN, Al-Jahdali H, Al-Ghanem S, et al. Reading chest radiographs in the critically ill (Part II): Radiography of lung pathologies common in the ICU patient. Ann Thorac Med. 2009;4(3):149–157. DOI:10.4103/1817-1737.53349

705 **Pleural effusions: Images A and B.** Before (A) and after (B) treatment. These images are a derivative work, adapted from the following source, available under : Toshikazu A, Takeoka H, Nishioka K, et al. Successful management of refractory pleural effusion due to systemic immunoglobulin light chain amyloidosis by vincristine adriamycin dexamethasone chemotherapy: a case report. *Med Case Rep.* 2010;4:322. DOI: 10.1186/1752-1947-4-322.

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707 **Pneumonia: Image B.** Lobar pneumonia, gross specimen. This image is a derivative work, adapted from the following source, available under : Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

707 **Pneumonia: Image C.** Acute inflammatory infiltrates in bronchopneumonia. This image is a derivative work, adapted from the following source, available under : Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

707 **Pneumonia: Image D.** Bronchopneumonia, gross specimen. This image is a derivative work, adapted from the following source, available under : Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

707 **Pneumonia: Image E.** Interstitial pneumonia. This image is a derivative work, adapted from the following source, available under : Allen CM, AL-Jahdali HH, Irion KL, et al. Imaging lung manifestations of HIV/AIDS. *Ann Thorac Med.* 2010 Oct-Dec; 5(4): 201–216. DOI: 10.4103/1817-1737.69106.

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708 **Lung abscess: Image B.** X-ray. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Yale Rosen.

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709 **Lung cancer: Image C.** Squamous cell carcinoma. This image is a derivative work, adapted from the following source, available under : Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .

709 **Lung cancer: Image E.** Large cell lung cancer. This image is a derivative work, adapted from the following source, available under : Jala VR, Radde BN, Haribabu B, et al. Enhanced expression of G-protein coupled estrogen receptor (GPER/GPR30) in lung cancer. *BMC Cancer.* 2012;12:624. doi 10.1186/1471-2407-12-624.

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710 **Superior vena cava syndrome: Images A and B.** Blanching of skin with pressure (A) and CT of chest (B). These images are a derivative work, adapted from the following source, available under : Shaikh I, Berg K, Kman N. Thrombogenic catheter-associated superior vena cava syndrome. *Case Rep Emerg Med.* 2013; 2013: 793054. DOI 10.1155/2013/793054.

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# About the Editors

### Tao Le, MD, MHS

Tao developed a passion for medical education as a medical student. He currently edits more than 15 titles in the *First Aid* series. In addition, he is Founder and Chief Education Officer of USMLE-Rx for exam preparation and ScholarRx for undergraduate medical education. As a medical student, he was editor-in-chief of the University of California, San Francisco (UCSF) *Synapse,* a university newspaper with a weekly circulation of 9000. Tao earned his medical degree from UCSF in 1996 and completed his residency training in internal medicine at Yale University and fellowship training at Johns Hopkins University. Tao subsequently went on to cofound Medsn, a medical education technology venture, and served as its chief medical officer. He is currently chief of adult allergy and immunology at the University of Louisville.

### Matthew Sochat, MD

Matthew practices general hematology/oncology in North Carolina. He completed his fellowship training in 2020 at St. Louis University in St. Louis, after an internal medicine residency at Temple University Hospital in Philadelphia. Matt earned his medical degree from the Warren Alpert Medical School of Brown University, and earned undergraduate degrees in biochemistry and the classics from the University of Massachusetts. Matt's pastimes include skiing, cooking and baking, traveling, the company of friends and loved ones (especially his wonderful wife), the Spanish language, and video gaming. Be warned: Matt also loves to come up with corny jokes at (in)opportune moments.

### Kristina Damisch, MD

Kristina earned a degree in mathematics from Lake Forest College in 2011 and had a brief career as a software development consultant in Chicago. She graduated from the University of Iowa Carver College of Medicine in 2020 and is applying to the 2021 Match for residency. She has a lifelong passion for emergency medicine with other strong interests including medical education and mental health. Outside of medicine, Kristina's family includes husband Kevin and cats Lemma and Kylo. She enjoys a wide variety of games, trivia, puzzles, escape rooms, trying new recipes, stargazing, and percussion.

### Connie Qiu, MD/PhD Candidate

Connie is in her final year of the MD/PhD program at the Lewis Katz School of Medicine at Temple University. She earned her bachelors degree at Johns Hopkins University, double majoring in molecular biology and philosophy. Connie's hard work is motivated by ensuring her dog a luxurious life. In her spare time, she enjoys mid-distance running, mountain hiking, modern art, movies, and memes. Her greatest achievement is winning a blue ribbon in the novice succulent category at the 2018 Philadelphia Flower Show. After medical school, she hopes to pursue a residency and academic career in dermatology.

### Vikas Bhushan, MD

Vikas is a writer, editor, entrepreneur, and teleradiologist on extended sabbatical. In 1990 he conceived and authored the original *First Aid for the USMLE Step 1*. His entrepreneurial endeavors included a student-focused medical publisher (S2S), an e-learning company (medschool.com), and an ER teleradiology practice (24/7 Radiology). Trained on the Left Coast, Vikas completed a bachelor's degree at the University of California Berkeley; an MD with thesis at UCSF; and a diagnostic radiology residency at UCLA. His eclectic interests include cryptoeconomics, information design, and avoiding a day job. Always finding the long shortcut, Vikas is an adventurer, knowledge seeker, and occasional innovator. He enjoys intermediate status as a kiteboarder and father, and strives to raise his three children as global citizens.

### Humood Boqambar, MB BCh BAO

Humood is an orthopedic assistant registrar in Kuwait. He earned his medical degree from the Royal College of Surgeons in Ireland and is pursuing a residency in orthopedic surgery in North America. Academically, Humood serves as a senior editor at ScholarRx and is passionate about medical education and peer-led teaching. In his spare time, Humood enjoys playing sports and is a CrossFit enthusiast. He is also an avid traveler and loves learning about countries' history, tradition, and culture.

### Jordan Abrams, MD

Jordan is a first-year anesthesiology resident at Mount Sinai West and Mount Sinai Morningside Hospitals in New York City. He graduated summa cum laude from St. George's University School of Medicine. Jordan is the founder and creator of theHYMedicine.com, an educational website that offers free medical study guides and resources for students worldwide. Aside from medicine, Jordan enjoys traveling, reading, soccer, and playing with his dog, Yara.

### Caroline Coleman, MD

Caroline is a first-year internal medicine resident at Emory University School of Medicine. She was a Foundation Fellow at the University of Georgia and earned a degree in economics before earning her medical degree at Emory, where she was a member of Alpha Omega Alpha honor society. She is interested in a career in critical care medicine, medical education, and investing in underserved populations. Caroline spends her free time hiking in the north Georgia mountains with her dog, Beau.

### Kimberly Kallianos, MD

Originally from Atlanta, Kimberly graduated from the University of North Carolina at Chapel Hill in 2006 and from Harvard Medical School in 2011. She completed her radiology residency and fellowship at UCSF and is currently an Assistant Professor of Clinical Radiology at UCSF in the Cardiac and Pulmonary Imaging section.